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Management of midtrimester prelabour rupture of membranes

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Management of midtrimester prelabour rupture of membranes

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Chapter 1

General introduction

Definitions and incidence

Fetal membranes surround the fetus and the amniotic fluid to form the amniotic cavity. 'Rupture of the membranes' is the medical term for 'the breaking of a woman's water'. When this occurs before labour starts, this is called prelabour rupture of the membranes (PROM). PROM happening before a gestational age of 37 weeks is called preterm prelabour rupture of membranes (PPROM). PPROM is a common obstetrical problem, since it is associated with adverse outcome for both the mother and the fetus. PPROM occurs in approximately 3% of all pregnancies, with reported incidences of 1,5%, 1% and 0,5% for PPROM between 34 and 37 weeks, 26 and 34 weeks, and 16 and 26 weeks gestational age, respectively[1]. The interval between 16 and 26 weeks is often referred to as the 'midtrimester'. Another term frequently used is periviable PROM, this is defined by rupture of membranes before 24 weeks. It can be estimated that midtrimester PROM occurs around 900 times per year in The Netherlands based on a total of around 180.000 deliveries.

Outcome after midtrimester PROM

Midtrimester PROM is associated with high perinatal mortality and morbidity. A meta-analysis of six studies showed a survival rate of almost 50% (122/275) in babies born after midtrimester PROM[2]. Unpublished data from a retrospective analysis by Van der Heijden et al. showed that in 164 singleton pregnancies with periviable PROM in three tertiary centres in The Netherlands, perinatal mortality was 71%. Since not all pregnancies with previable PROM will be referred from second line hospitals, this might be an underestimation[3]. The main causes of adverse outcome are prematurity, pulmonary hypoplasia and infection.

Prematurity

Since midtrimester PROM occurs near the limit of viability, outcome is greatly determined by the consequences of extreme prematurity. Muris and Girard reported that 38% of women delivered within one week, and 69% delivered within 5 weeks after PROM before 25 weeks[4]. Perinatal mortality rates per gestational age at delivery from the Dutch perinatal registry (PRN) between 2000 and 2006 in the Netherlands are shown in Figure 1.1[5].

Preterm birth causes acute problems as IRDS (infant respiratory distress syndrome), intraventricular haemorraghe (IVH), necrotizing enterocolitis (NEC), sepsis, whilst bronchopulmonary dysplasia (BPD), cerebral palsy (CP) and other disabilities complicate long term outcome[2,6]. Long term data on outcome after very preterm birth in Europe have recently been reviewed by Milligan[7].

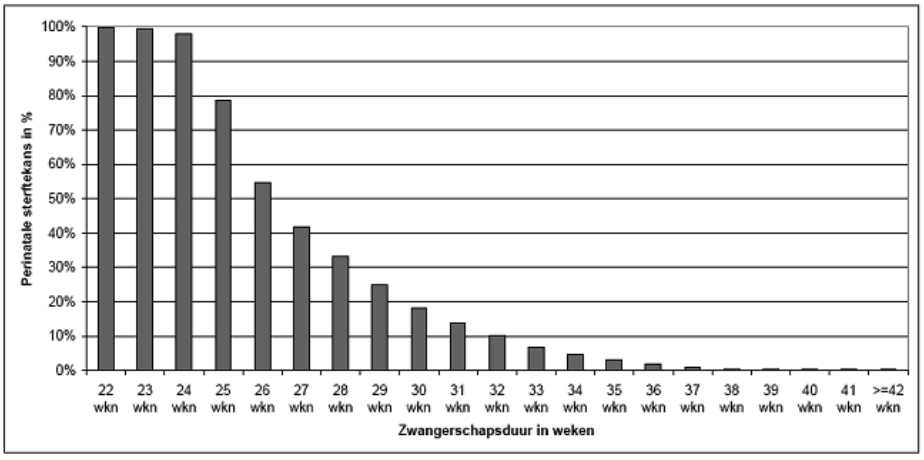

Figure 1.1 Perinatal mortality per gestational age at delivery. Dutch perinatal registry (PRN) between 2000 and 2006, n=1257026.

Pulmonary hypoplasia

Midtrimester PROM is associated with an increased risk of altered pulmonary development leading to pulmonary hypoplasia. Pulmonary hypoplasia is a term to describe pulmonary underdevelopment. It is characterised by an inadequate formation of the respiratory tree resulting in a reduced amount of functional lung tissue, with reduced capacity for gas exchange[8].

It is thought that the formation of lung tissue is dependent on an adequate amount of amniotic fluid, especially during the interval between 16 and 26 weeks. A reduced amount of amniotic fluid (oligohydramnios) after PROM in this interval might cause pulmonary hypoplasia[9].

Pulmonary hypoplasia can present as severe breathing problems resulting in early neonatal death or as milder and even transient breathing problems. It can be accompanied by bleeding in the lung. It can also result in chronic breathing problems due to scarring of lung tissue[8].

In a review of 11 studies on midtrimester PROM, the reported incidence of pulmonary hypoplasia secondary to midtrimester PROM ranged widely from 1 to 48%[10]. In another review the reported incidence also varied widely from 0 to 24%[9]. Since IRDS, BPD and pneumonia can occur simultaneously, a clinical diagnosis without autopsy is difficult.

Infection

It is estimated that 40-70% of cases of preterm births with PROM or spontaneous labour are complicated by chorioamnionitis[11]. The association of infection with

spontaneous preterm birth is stronger, the earlier preterm delivery occurs. Infection can be either the cause or the result of PPROM. It is becoming more and more clear that chorioamnionitis in fact is a major risk factor for preterm birth, rather than a consequence[12-14].

Ascending infection from the lower genital tract can cause a maternal and fetal inflammatory response with activation of matrix metallopproteinases (MMP's) and cytokines and apoptosis, after which PPROM can occur. Histological studies suggest that rupture occurs near the site of inflammation[14].

Infection may manifest itself as a clinical chorioamnionitis (with or without labour and PPROM), once a maternal inflammatory response can be clinically noticed. Clinical chorioamnionitis is diagnosed by fever, uterine tenderness, maternal and or fetal tachycardia, and purulent or foul amniotic fluid. Maternal complications are endomtetritis, wound infection, pelvic abcess, sepsis and haemorrage. Severe maternal morbidity or even fatal outcome is rare[11].

Only a minority of cases with chorioamnionitis will present with clinical symptoms. Subclinical infection is thought to influence neonatal outcome, however the exact magnitude of this influence remains unclear[15].

Subclinical or clinical chorioamnionitis may initiate a fetal inflammatory respons (FIRS). In cases where chorioamnionitis is present, FIRS is thought to be an important determinant of severe adverse neonatal outcome[16].

Presence of subclinical infection can be diagnosed by pathological examination of the placenta postnatally (histological chorioamnionitis), or by microbiological examination of placental tissue or amniotic fluid. FIRS can be diagnosed postnatally by biochemical test (cytokine response) or histologically by vasculitis in the chorion or umbilical cord (funisitus). Clinical usefulness is limited since it may take several days before the results of such examination become available. Furthermore, with current conventional culturing techniques intrauterine infection is difficult to detect[17]. It is important to note that there is only a limited overlap between histological, microbiological or biochemical and clinical chorioamnionitis[18].

Thus a substantial part of midtrimester PROM is associated with subclinical infection, and FIRS can be subclinically present, causing long term morbidity.

Factors associated with adverse outcome

Oligohydramnios, gestational age at rupture, latency, gestational age at delivery are factors that have been studied to predict adverse outcome in cases amenable for expectant management.

Oligohydramnios in cases of PPROM is associated with increased mortality and morbidity. Perinatal mortality in a group of 178 prospectively followed pregnancies with PPROM between 20-25 weeks, and delivery after 26 weeks gestational age was

2,1% in cases with adequate amniotic fluid, versus 69% in cases with inadequate amniotic fluid. Oligohydramnios is associated with shorter intervals from gestational age at PPROM to delivery[19]. Pulmonary development is impaired by oligohydramnios , and risk of chorioamnionitis and contractures is increased[20,21].

It has been observed that earlier **gestational age at rupture** increases risk of pulmonary hypoplasia[22]. Earlier gestational age at rupture is associated with increased risk of infection. Furthermore, obviously an earlier gestational age at rupture predisposes to a periviable delivery, with increased risks due to immaturity or prematurity.

Regarding **latency**, i.e. the time interval between PROM and the actual delivery, controversy exists. The effect of gestational age on latency is not clear, some authors observed that earlier gestational ages at ROM is followed by relatively shorter latencies[23], whereas others observe longer latencies after earlier gestational age at rupture[24,25]. The key question regarding to latency is however, if, a longer stay in a possibly unfavourable environment is hazardous, and should be considered apart from the gestational age of delivery.

It has been observed that cases with shorter latencies are more frequently associated with chorioamnionitis. The highest frequency has been observed in the first week after rupture. This is not a surprise since subclinical infection is a known cause of preterm labour. For those fetuses that remain undelivered, the question is how the risk of chorioamnionitis will evolve with increasing length of latency.

A study that stratified for gestational age at delivery showed that longer latencies after PPROM between 28 and 34 weeks were associated with in increased risk for adverse outcome. Apparently the benefit of increased maturity outweighed the risks associated by prolonged latency[26].

To date no such studies have been published for midtrimester PROM. However it can be hypothesized that the same principle applies, that is, an overall beneficial effect of longer latency.

Not surprisingly, **gestational age at delivery** is most predictive of favourable outcome in infants born at the threshold of viability for various indications[27].

Impact

Pregnancies complicated by midtrimester PROM are associated with high immediate and long-term costs. These are caused by extended maternal hospital admissions, increased incidence of premature delivery, and frequent neonatal complications hereafter requiring NICU-admission. At the long term, disabilities in survivors can have a life-long impact.

For early preterm delivery (<32 weeks' gestation) occurring in only 1–2% of total births, it is estimated that it accounts for nearly 50% of all longterm neurological morbidity[28]. For midtrimester PROM, having a higher perinatal mortality, this might be different.

Studies with long term follow up are scarce. In a study by Pristauz on neonatal outcome after 2 years, from a group of 71 fetuses that were expectantly managed after spontaneous PROM <25 weeks, 12 infants could be discharged alive. Of these 12, 6 had normal neonatal outcome at 2 years[29].

Diagnosis of ROM

In approximately 90% of cases the diagnosis of ROM can be based on a history of fluid loss, combined with ultrasound and or speculum examination. Digital examination is to be avoided, since it increases the risk of infection. Speculum examination allows for visualisation of fluid passing from the cervix and for examination of this fluid using a nitrazine test or a microscope to visualize ferning[30]. These tests together are called 'conventional testing'.
It has been claimed that this clinical approach has a significant false-negative rate of 12%[31]. Furthermore, false positive tests are common, due to vaginal contamination with blood, urine, or semen[32-35].
The inaccuracy of the conventional test and the intrusive nature of a speculum examination have prompted many investigators to develop new tests to diagnose rupture of membranes.

Management of midtrimester PROM

General principles

Midtrimester PROM is a worrisome clinical situation. Until the 1990's, termination of pregnancy was usually offered to patients, obstetricians fearing maternal infectious morbidity, and estimating the probability of favourable outcome as minimal. Since the 1990's, expectant management of very early PROM became more acceptable, with the advantages brought by improvement of neonatal care, outweighing the maternal risks[36].
Expectant management of PPROM can be considered in cases where complications (labour, chorioamnionitis or abruption) are not manifest. This management varies internationally, but usually consists of hospitalization at the border of viability and administration of intramuscular corticosteroids and antibiotics to prolong latency. When expectant management can be considered as an option, counselling should take place. Parents should be informed about the risks of extreme prematurity, and on the risks of a prolonged stay in utero. Surveillance during expectant management is aimed at preterm birth, (sequels of) infection, and pulmonary hypoplasia, being the main

causes of perinatal mortality. Abruptio placentae, prolapse and or compression of the umbilical cord are other complications that can occur during expectant management.

Current management and surveillance of PPROM

Corticosteroids, tocolytics and antibiotics

Although corticosteroids in women at risk for preterm birth (including those with PPROM) have proven beneficial from 26 weeks gestational onwards, there is no evidence from randomised controlled trials that prove corticosteroids to be beneficial before 26 weeks. However, there also is no proven harm[37]. In a review by Waters and Mercer four non-randomised studies were found that reported on survival according to steroid exposure. Although subject to bias, a significant benefit seemed apparent[2].
The American Congress of Obstetrics and Gynaecology recommends a single course of corticosteroids for PPROM, after 24 weeks[38]. The long term effects of corticosteroids in cases with chorioamnionitis specifically remains to be elucidated[39].
The use of profylactic tocolyics is controversial[2]. Regarding antibiotics the same applies. Extrapolation from short term benefit observed in randomized studies such as the Oracle study, has led to the recommendation to administer broad spectrum antibiotics from 24 weeks onwards. In the Oracle study approximately 10% of included women had PROM before 26 weeks, however there was no subgroup analysis[40]. The Dutch guideline as well as the guideline from the United Kingdom do not specify a lower border of gestational age at which corticosteroids and antibiotics are recommended[1,41].
For antibiotic treatment in case of a Group B positive culture, the same applies.
One RCT reported on weekly progesteron in cases of PPROM between 20 and 30 weeks and found no benefit[42].

Non-traditional therapies

Several therapies have been evaluated with the goal of normalizing the fluid volume in the amniotic cavity. Sealing of the membrane defect to prevent further leaking was attempted by several investigators. However, series were small and control groups were absent[2].
Another way to relieve oligohydramnios after PPROM is amnioinfusion, a more extensively studied strategy. Amnioninfusion might improve fetal outcome by preventing pulmonary hypoplasia, by preventing neurological complications, increasing time to delivery interval, and improving fetal biophysical profile through prevention of umbilical cord compression. It also might prevent fetal deformity[43].
A recent meta-analysis concluded that there might be benefit in amnioinfusion for oligohydramnios secondary to early PPROM. However, this meta-analysis found only 2 RCT's and 1 quasi RCT as well as 4 observational studies. The 2 RCT's were on patients

with PPROM after 24 weeks, the quasi randomised study was on midtrimester PPROM[44].

Predicting preterm delivery

Cervical length in PPROM is currently not used to direct management of PPROM. International guidelines vary. Berghella et. al. investigated if knowledge of cervical length improved management of PPROM but found no results[45].
Recently, Cobo et. al. measured 24 inflammatory biomarkers in 60 women with PPROM between 22 and 34 weeks and found no predictive value for preterm delivery within 1 week[46]. Similarly Mercer et al did not find useful predictive value of maternal plasma markers[47].

Prediction of chorioamnionitis

As specified before, there is limited overlap of clinical, histological, and microbiological chorioamnionitis. Ultimately prediction of FIRS and or neonatal sepsis is of key importance for clinical management. Maternal complications of chorioamnionitis are not considered here.
During expectant management, inflammatory markers indicative of intra amniotic infection can give rise to systemic effects, or local effects. Clinical parameters as well as laboratory tests (blood, amniotic fluid, cervicovaginal secrtetions) are available instruments to investigate this.
Clinical parameters needed to establish the diagnosis of clinical chorioamnionitis used in clinical research are antepartum temperature at least 100.4°F, in addition to two other signs (uterine tenderness, maternal or fetal tachycardia and foul/purulent amniotic fluid), although these criteria are not uniformely used[11,47].
These individual parameters generally have low specificity, and limited sensitivity. When clinical signs are not conclusive or absent, and chorioamnionitis is suspected, for example in case of PPROM or preterm labour, serum and amniotic fluid can be tested.
Determination of white blood cell count (leucocytes) and C-reactive protein (CRP) is being used to assess evidence of infection. However, one might question this since an elevated CRP and or leucocytosis in case of PPROM is a non-specific finding in absence of other clinical signs.

Prediction of pulmonary hypoplasia

An assessment of the probability of pulmonary hypoplasia is important both for clinical decision making and counselling of patients. It has been attempted to predict pulmonary hypoplasia using clinical parameters - gestational age at PPROM, latency period and degree of oligohydramnios – as well as biometric parameters assessed by

ultrasound (two- or three dimensional, Doppler) or MRI. If presence of lethal pulmonary hypoplasia seems very likely, expectant management may be reconsidered.

Aims of this thesis

This thesis deals with the following questions:

- What is the true prognosis of midtrimester PPROM, and what is the role of longer latency? (chapter 2).
- What is the value of several diagnostic tests used to diagnose PROM? (chapter 3).
- Does determination of C-reactive protein and leucoytes make sense in surveillance of expectant management during PPROM, in order to predict neonatal infectious disease? (chapter 4).
- What is the predictive value of clinical- and imaging parameters in women at risk of pulmonary hypoplasia after midtrimester PPROM? (chapters 5 and 6).
- Does serial transabdominal amnioinfusion improve outcome after midtrimester PPROM? (chapters 7 and 8).

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Chapter 2

The relation between duration of ruptured membranes and perinatal outcome in patients with midtrimester prelabour rupture of membranes

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Schaaf JM, Ravelli A, Pajkrt E, Willekes C, Nijhuis JG, Mol BW

Submitted

Abstract

Objective
To assess impact of gestational age at rupture and latency on perinatal outcome after midtrimester PROM.

Study design
We obtained data on singleton pregnancies from 22 weeks onwards from the Dutch Perinatal Registry from 1999 to 2007, congenital abnormalities were excluded. In women with PPROM before 26 weeks, we studied impact of gestational age at rupture and latency on perinatal mortality and severe morbidity.

Results
From 1,445,305 pregnancies, 1,233 suffered midtrimester PROM. Higher gestational age at delivery increased the probability of survival without morbidity, but the moment at which PPROM had occurred did not. For babies born between 24-26, 26-28, 28-30, 30-34 and after 34 weeks, perinatal mortality rates were 70%, 26%, 14%, 6% and 2%, respectively. The perinatal mortality rate for babies born after PPROM between 16-18 weeks was 26%, for babies born after PPROM between 18-20, 20-22, 22-24 and 24-26 this was respectively 29%, 52%, 66% and 33%.
Morbidity free survival rates were 5%, 13%, 25%, 36% and 95% for babies born between 24-26, 26-28, 28-30, 30-34 and after 34 weeks. For babies born after PPROM between 16-18, 18-20, 20-22, 22-24 and 24-26 these rates were 68%, 60%, 31%, 21% and 27% respectively. Sepsis occurred in 45% of children born between 24 and 32 weeks, but occurred in 2% born after 34 weeks.

Conclusion
Midtrimester PROM is associated with increased mortality and morbidity, but longer latency and early gestational age at PPROM have limited impact in patients delivering after 22 weeks.

Introduction

Midtrimester PPROM occurs in approximately 0,5 to 1% of all pregnancies and is associated with poor perinatal outcome[1]. If after midtrimester PPROM imminent delivery does not occur, discussion of the possible outcome is part of patient counselling. Based on the information provided, parents will have to decide between expectant management and, if they want to avoid the risk of perinatal morbidity and mortality, immediate delivery by means of termination of pregnancy. However, data that could be used in counselling are mainly from small heterogeneous studies and difficult to interpret.

A meta-analysis of six of those studies showed a survival rate of almost 50% (122/275) in babies born after midtrimester PPROM [2]. Among surviving infants, morbidity is high and includes (sequels of) premature delivery, pulmonary hypoplasia, infection, growth retardation and restriction deformities[2,3]. Gestational age at delivery has a profound effect on outcome if one considers the periviable period[4], longer latency (i.e., the interval between rupture of membranes and delivery) thereby having a favourable effect .

Obviously, at the moment of counselling, latency is unknown. Reports on median latency after midtrimester PPROM vary, with contradictory relationships between the moment at which PPROM occurs, and latency[5-7].

The relationship between latency after very early PPROM and outcome is complex. A longer latency after very early midtrimester PPROM theoretically decreases the risk associated with prematurity. However, it is also debated that longer latency carries a higher risk of pulmonary hypoplasia, a condition associated with high mortality, especially if oligohydramnios is also present[8-10]. Pulmonary hypoplasia has been described after a latency of only 6 days[11]. Furthermore, prolonged exposure to subclinical chorioamnionitis might worsen the outcome[12].

Thus, counselling of patients with midtrimester PPROM remains challenging. The aim of this study was to provide data on perinatal outcome after midtrimester PPROM in patients who delivered after 22 weeks by extracting data from the Dutch Perinatal Registry (PRN). Furthermore we assessed the effect of latency and gestational age at PPROM on outcome by stratification of gestational age at delivery and gestational age at PPROM.

Materials and methods

We studied data collected by the PRN between 1999 and 2007. These data contain detailed population-based information, collected by prenatal caregivers, on pregnancies, deliveries, and (re)admissions until 28 days after delivery. Source data are available from three independent registries: the midwifery registry (LVR1), the obstetric

registry (LVR2) and the neonatology/pediatric registry (LNR).The midwifery and obstetric registries start at the booking visit and contain complete perinatal data from 22^{+0} gestational weeks onwards. The neonatology registry contains only data on hospital admissions of newborns. These databases are then combined into one nationwide perinatal database via a validated linkage method[13]. The PRN registry covers 96% of all births in the Netherlands[14].

We included all singleton pregnancies with a gestational age at delivery starting from 22^{+0} gestational weeks onwards. Women with pregnancies with congenital abnormalities (2.4%) were excluded as well as women with a multiple pregnancy (3.9%). We selected all cases with a rupture of membranes before 26^{+0} weeks, with a minimum latency of 24 hours. Rupture of membranes was diagnosed based on history and clinical findings such as gross vaginal fluid loss, in combination with other available diagnostic test methods when necessary. The final decision on whether a patient had rupture of membranes or not was made by the attending staff.

As outcome measurements we studied both perinatal mortality during the first 4 weeks after birth as well as severe neonatal morbidity. Perinatal mortality was defined as the number of fetal deaths (stillbirths) and neonatal deaths in the first four weeks of life per 1000 total births. Severe morbidity was defined as a composite of IVH (intraventricular haemorrhage), BPD (bronchopulmonary dysplasia) or IRDS (infant respiratory distress syndrome), neonatal sepsis or Apgar score after 5 minutes <7. A part of these composite morbidity outcome measurements were defined at the hospital admission of the child by the neonatologist, and occurred in the same admission after birth or during a re-admission within the first four weeks of life. Perinatal survival was defined as the absence of perinatal mortality. The PRN does not record long term neonatal outcome. First the baseline characteristics, as far as these were available from the PRN database, were described. Subgroup analysis: Since not all hospitals with neonatal care register in the LNR, we repeated the analysis limited to the hospitals who registered during at least 2 or more years during the study period.

Results

From a population of 1,445,305 pregnancies registered, from 1999 to 2007, 1,233 patients with singleton pregnancies complicated by midtrimester rupture of membranes, delivered after 22 weeks (Figure 2.1).

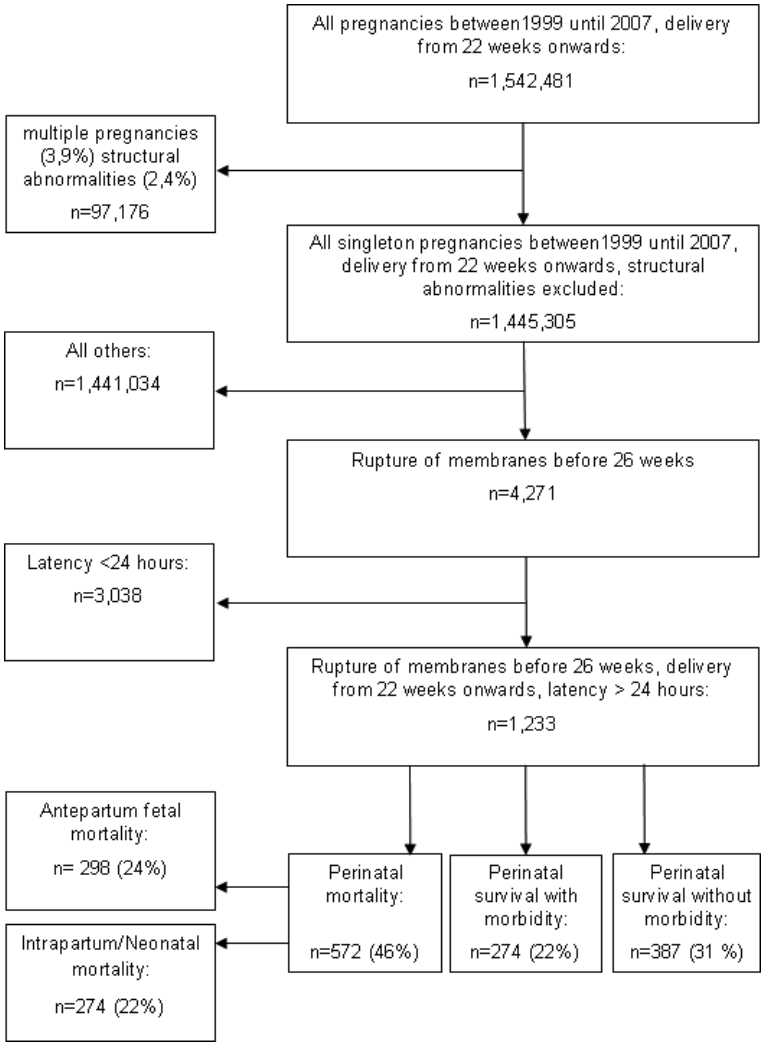

Figure 2.1 Patient enrollment.

Maternal demographics and characteristics are listed in Table 2.1. Factors possibly affecting outcome like ante partum bleeding, amniocentesis and history of preterm birth were non-obligatory variables in the PRN database, and were therefore not included in this table.

The overall perinatal mortality was 572 from 1233 (46,4%). There were 298 cases of stillbirth (24,2%), while 274 babies died intrapartum or postpartum (22,2%). Perinatal

survival with morbidity occurred in 274 (22,2%) children, while 387/1233 (31,4%) survived without severe morbidity (Figure 2.1).

Table 2.1 Maternal and fetal demographics and characteristics.

	Patients experiencing perinatal death or neonatal morbidity (n=846)	Perinatal survival without morbidity (n=387)	P value
Maternal characteristics			
Maternal Age (yrs)	30.6	30.5	0.8
Caucasian (n)	623 (74%)	292 (75%)	0.52
Nulliparous (n)	373 (44%)	154 (40%)	0.17
Fetal characteristics			
Fetal Birthweight (grams)	805	2905	<0.0001
Fetal gender male (n)	455	199	0.46

One or more items of the composite morbidity were present in 759 of 1233 patients. In 485 of cases of mortality on or more items of morbidity were present. 278 suffered from sepsis, in 550 infants there was an apgar score after 5 minutes <7. 223 suffered from IRDS, 106 from BPD, in 58 cases IVH was present.

More advanced gestational age at delivery increased the probability of survival, but a more advanced moment at which PPROM occurred did not.(Table 2.2). For babies born between 24-26, 26-28, 28-30,30-32 and 32-34 weeks the survival rates were 30%, 74%, 86%, 93% and 95% respectively. Above 34 weeks, survival was above 98%. For all babies delivered after 22 weeks, if PPROM occurred at 16-18 weeks survival was 74%, in the groups with PPROM at 18-20, 20-22, 22-24 and 24-26 weeks this was 71%, 48%, 34% and 67%, respectively.

Table 2.2 Patients surviving by gestational age of delivery and PROM.

GA at delivery	GA at ROM in weeks					
in weeks	$16^{+0}-17^{+6}$	$18^{+0}-19^{+6}$	$20^{+0}-21^{+6}$	$22^{+0}-23^{+6}$	$24^{+0}-25^{+6}$	**All**
$22^{+0}-23^{+6}$	0% (0/9)	0% (0/18)	1% (1/93)	1% (2/194)	NA	**0% (3/314)**
$24^{+0}-25^{+6}$	0% (0/4)	25% (3/12)	22% (2/9)	17% (15/90)	37% (63/166)	**30% (83/281)**
$26^{+0}-27^{+6}$	0% (0/4)	33% (1/3)	80% (12/15)	85% (18/20)	74% (93/125)	**74% (123/167)**
$28^{+0}-29^{+6}$	100% (2/2)	66% (2/3)	85% (11/13)	93% (14/15)	84% (27/32)	**86% (56/65)**
$30^{+0}-31^{+6}$	100% (2/2)	100% (4/4)	89% (8/9)	100% (10/10)	88% (15/17)	**93% (39/42)**
$32^{+0}-33^{+6}$	100% (3/3)	80% (4/5)	100% (12/12)	83% (5/6)	100% (18/18)	**95% (42/44)**
$34^{+0}-35^{+6}$	100% (1/1)	NA (0/0)	100% (5/5)	100% (4/4)	100% (16/16)	**100% (26/26)**
$\geq 36^{+0}$	94% (50/53)	98% (66/67)	98% (46/47)	100% (71/71)	100% (56/56)	**98% (289/294)**
All	**74% (58/78)**	**71% (80/112)**	**48% (97/203)**	**34% (138/410)**	**67% (288/430)**	**54% (661/1233)**

GA: Gestational age. ROM: rupture of membranes. NA: not applicable.

Similarly, a more advanced gestational age at delivery increased the probability of survival without severe morbidity (Table 2.3). For babies born between 24-26, 26-28, 28-30 30-32, 32-34 and after 34 weeks, the morbidity free survival rates were 5%, 13%,

25%, 31%, 41% and 98%, respectively. For all babies born after 22 weeks, morbidity free survival was 48% when PPROM had occurred at 16-18 weeks. In the groups with PPROM at 18-20, 20-22, 22-24 and 24-26 weeks this was 60%, 31%, 21% and 27%, respectively. There was no sign that earlier gestational age at PPROM was related to adverse outcome. Morbidity free survival as a percentage of all survivors is shown as well. For the groups with PPROM at 16-20, 18-20, 20-22, 22-24 and 24-26 weeks this was 65%, 84%, 65%, 62% and 41% respectively. In all survivors 58% were without severe morbidity.

Table 2.3 Patients surviving without severe morbidity, as a percentage of all, and as a percentage of all survival

GA at delivery in weeks	GA at ROM in weeks $16^{+0}-17^{+6}$	$18^{+0}-19^{+6}$	$20^{+0}-21^{+6}$	$22^{+0}-23^{+6}$	$24^{+0}-25^{+6}$	**All**
$22^{+0}-23^{+6}$	0% (0/9)	0% (0/18)	0% (0/93)	0% (0/194)	NA	**0% (0/314)**
$24^{+0}-25^{+6}$	0% (0/4)	0% (0/12)	0% (0/9)	1% (1/90)	7% (12/166)	**5% (13/281)**
$26^{+0}-27^{+6}$	0% (0/4)	0% (0/3)	20% (3/15)	20% (4/20)	12% (15/125)	**13% (22/167)**
$28^{+0}-29^{+6}$	100% (2/2)	0% (0/3)	15% (2/13)	27% (4/15)	25% (8/32)	**25% (16/65)**
$30^{+0}-31^{+6}$	50% (1/2)	25% (1/4)	44% (4/9)	30% (3/10)	24% (4/17)	**31% (13/42)**
$32^{+0}-33^{+6}$	0% (0/3)	20% (1/5)	42% (5/12)	17% (1/6)	61% (11/18)	**41% (18/44)**
$34^{+0}-35^{+6}$	100% (1/1)	NA (0/0)	80% (4/5)	75% (3/4)	75% (12/16)	**77% (20/26)**
$\geq 36^{+0}$	92% (49/53)	97% (65/67)	96% (45/47)	99% (70/71)	100% (56/56)	**97% (285/294)**
All (severe morbidity free survival)	**68% (53/78)**	**60% (67/112)**	**31% (63/203)**	**21% (86/410)**	**27% (118/430)**	**31% (387/1233)**
All (severe morbidity free survival as a % of survival)	**91% (53/58)**	**84% (67/80)**	**65% (63/97)**	**62% (86/138)**	**41% (118/288)**	**58% (387/661)**

GA: Gestational age. ROM: rupture of membranes. NA: not applicable.

From all 78 women who suffered PPROM between 16 and 18 weeks and reached 22^{+0} weeks, 54 patients delivered after 34 weeks (69%). For the women suffering PPROM at 18-20, 20-22, 22-24 and 24-26 weeks this was 60%, 26%, 18% and 17%, respectively. Sepsis occurred in 45% of children born between 24 and 32 weeks, but occurred in five of 320 infants born after 34 weeks (2%). (Table 2.4). Analysis of the neonatal outcomes limited to the hospitals who registered during at least 2 or more years during the study period yielded similar results (data not shown).

Table 2.4 Prevalence of sepsis by gestational age of delivery and gestational age of PROM.

GA at delivery in weeks	GA at ROM in weeks $16^{+0}-17^{+6}$	$18^{+0}-19^{+6}$	$20^{+0}-21^{+6}$	$22^{+0}-23^{+6}$	$24^{+0}-25^{+6}$	**All**
$22^{+0}-23^{+6}$	0% (0/9)	0% (0/18)	1% (1/93)	1% (2/194)	NA	**1% (3/314)**
$24^{+0}-25^{+6}$	0% (0/4)	17% (2/12)	22 (2/9)	19% (17/90)	34% (56/166)	**27% (77/281)**
$26^{+0}-27^{+6}$	50% (2/4)	33% (1/3)	53% (8/15)	50% (10/20)	70% (88/125)	**65% (109/167)**
$28^{+0}-29^{+6}$	0% (0/2)	66% (2/3)	77% (10/13)	67% (10/15)	63% (20/32)	**65% (42/65)**
$30^{+0}-31^{+6}$	50% (1/2)	75% (3/4)	33% (3/9)	50% (5/10)	65% (11/17)	**55% (23/42)**
$32^{+0}-33^{+6}$	100% (3/3)	20% (1/5)	50% (6/12)	33% (2/6)	39% (7/18)	**43% (19/44)**
$34^{+0}-35^{+6}$	0% (0/1)	NA (0/0)	20% (1/5)	25% (1/4)	13% (2/16)	**15% (4/26)**
$\geq 36^{+0}$	0% (0/53)	1% (1/67)	0% (0/47)	0% (0/71)	0% (0/56)	**0% (1/294)**
All	**8% (6/78)**	**9% (10/112)**	**15% (31/203)**	**11% (47/410)**	**43% (184/430)**	**23% (287/1233)**

GA: Gestational age. ROM: rupture of membranes. NA: not applicable.

Discussion

In this study, we found increased mortality and morbidity rates in patients with PPROM delivering after 22 weeks. In these patients, longer latency and early gestational age at PPROM have limited impact.

To our knowledge, this is the largest study on outcome after midtrimester PPROM. Similarly to Manuck et al, we stratified outcome on the basis of both gestational age at rupture of membranes, and gestational age at delivery[4,15]. This approach allows counseling of women that have reached a certain gestational age following very early PPROM, and a more straightforward comparison of different latencies and their influence on outcome.

The use of the PRN data however has limitations. Outcome on patients with midtrimester PPROM who deliver prior to 22 weeks is not registered. Counseling women with PPROM at 20 weeks gestational age remains therefore difficult, as data on median latency after PPROM at for example 16 weeks cannot be given.

A second important limitation is the absence of data on oligohydramnios, a known predictor of adverse outcome. In a study by Hadi et al.[16], 98% survival was seen in 91 patients admitted with PPROM between 20 and 25 weeks of gestational age, when there was a fluid pocket larger than 2 cm, versus 31% of 13 patients with a pocket less than 2 cm, in a group delivering at similar gestational age. Overall, reports on the actual incidence of oligohydramnios after midtrimester PPROM and its exact influence on outcome are scarce[17].

The definition of severe morbidity that we used might also be subject of debate. Figures on pulmonary hypoplasia, restriction deformities, necrotizing enterocolitis and periventricular leukomalacia could not be included for example. Moreover, to our knowledge long term follow up on patients registered in the PRN during our study interval so far is absent.

Borgida et al. found a 1% rate of PPROM after amniocentesis, with significantly longer latencies and better perinatal outcomes compared with outcomes after spontaneous PPROM at a similar gestational age[18]. It is not clear how this phenomenon has affected outcome in our study, nor are data available on amniocentesis prior to PPROM.
Information about the incidence of termination of pregnancy is missing as well, as this is a non-obligatory variable in the PRN. It is possible that due to pregnancy terminations bad outcome is being underestimated, since in patients with risk factors such as anhydramnion or vaginal bleeding termination of pregnancy might seem more appropriate.
Midtrimester PPROM is a worrisome clinical situation. Termination of pregnancy is offered to patients if the perinatologist estimates that the probability of favorable outcome is minimal. If expectant management is an option, counselling parents on chances of survival without severe morbidity is important, but difficult due to limitations in quality and quantity of available data.
An overview of studies on perinatal survival published from 2000 onwards after very early PPROM is shown in Table 2.4. The available data are likely to be biased by the fact that patients not amenable to continued expectant management are often excluded (i.e. bleeding, labour, stillbirths, pregnancy terminations in patients with structural abnormalities), and therefore survival is likely to be overestimated[2].
The studies shown in this overview present mostly small series and differ in minimal latency included as well as in other inclusion criteria, such as multiple pregnancies. Median gestational age at time of rupture of membranes varies, and management schemes are not uniform.

Adverse outcome after midtrimester PPROM is mainly determined by prematurity, pulmonary hypoplasia, infectious disease and deformities[3]. Persistent oligohydramnios during the midtrimester has extensively been described as a poor prognostic sign[3,8]. Gestational age at PPROM, oligohydramnios and latency are known factors predicting pulmonary hypoplasia, though doubt remains whether latency is a predictor independent of gestational age at PPROM[17].
Furthermore it has been hypothesized that expectant management increases the risk of development of chorioamnionitis and sepsis, with subclinical intrauterine infection contributing to this risk as well as to other neonatal morbidities such as periventricular leuko-malacia, intraventricular hemorrhage, cerebral palsy pulmonary hypoplasia and bronchopulmonary dysplasia[12,19]. In our data, early PPROM and thus longer latency did not increase chances of adverse outcome for any gestational age at delivery once 22^{+0} weeks of gestation has been reached.

Regarding sepsis our findings are in line with existing literature. Chorioamnionitis is strongly associated with shorter latencies, with highest incidences reported between two and five days after rupture of membranes[20]. Consequently, neonatal sepsis - as a

sequel of chorioamnionitis - could be expected to occur more frequently in pregnancies with shorter latencies (Table 2.4).
Careful interpretation of solid data should replace subjective factors. Our study provides figures on outcome after midtrimester PPROM for patients with a certain gestational age of at least 22 weeks. Our study suggests that there does not seem to be a detrimental effect of longer latency nor early gestational age on perinatal outcome in patients once they reach 22 weeks. Therefore, after 22 weeks, these factors should not be used as an argument to terminate the pregnancy. Even before 22 weeks, where imminent delivery in a supposedly large group will lead to an almost certain perinatal mortality, expectant management is a reasonable course given the high percentage of morbidity free survival in the ones who do survive. There is a need for similar data on outcome before 22 weeks gestational age.

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Chapter 3

Prelabour rupture of membranes:

overview of diagnostic methods

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Abstract

Purpose of review
To evaluate diagnostic accuracy studies for rupture of the fetal membranes (ROM)

Recent findings
Sample sizes of recent studies are small and studies used different “silver standard” definitions for ROM. Therefore, reported results should be interpreted with caution. Over the review period the focus of diagnostic studies has been on two bedside test strips: insulin-like growth factor-binding protein-1 (IGFBP-1) and placental alpha microglobulin-1 (PAMG-1). Bedside tests improve the confidence of the clinician about their diagnosis. Compared to nitrazine or ferning test alone, IGFBP-1 and PAMG-1 are more accurate. However, compared to the conventional testing (combination of history, ferning, nitrazine, speculum and ultrasound) no statistical difference in accuracy was found. In vitro PAMG-1 is shown to be superior to IGFPB-1. Furthermore, soluble intercellular adhesion molecule-1 (sICAM-1) and Axl receptor tyrosine kinase (Axl) seem to be promising new specific biomarkers for diagnosing ROM.

Summary
IGFBP-1 and PAMG-1 are the most commonly used bedside test for diagnosing ROM. Both tests seem to be sensitive and specific, however evidence is lacking especially in equivocal cases and comparative studies against the real golden standard (amnio-dye) have still not been published. Further effectiveness research is needed before tests can be applied in practice.

Introduction

Prelabour rupture of the fetal membranes (PROM) complicates 5 to 10% of all pregnancies[1,2] and it is associated with an increased incidence of chorioamnionitis, prematurity and with increased perinatal and maternal morbidity and mortality[3]. In the majority of women, the diagnosis of ruptured fetal membranes can be based on a history of PROM with speculum examination. This clinical approach has, however, a 12% false-negative rate[4]. In approximately 10% of all cases, the diagnosis of rupture of membranes is difficult to establish[5,6].

In order to improve the accuracy to diagnose PROM a wide variety of tests have been introduced, the first one to be alkaline testing introduced in the 1930s[7]. For decades, a combination of visual pooling of amniotic fluid during speculum examination, alkaline pH determination and microscopic evidence of ferning and decreased amniotic fluid by ultrasound has been widely used to determine rupture of membranes. This combination has been referred to as “conventional testing”. These tests, however, are prone to false positive results secondary to vaginal contamination with blood, urine, or semen[5,8-10].

Besides the inaccuracy of the conventional test, many women find the use of a speculum examination intrusive[11]. In order to improve the accuracy of diagnostic test and simplify test procedures without the use of a speculum, dozens of tests have been developed over the last decades. In this review, we highlight and report the diagnostic accuracy studies on diagnostic test for PROM that have been published since a systematic review on diagnostic methods for rupture of the fetal membranes in equivocal cases[12*].

Systematic review

We performed a systematic review to assess the accuracy of several tests for the diagnosis of ROM in equivocal cases[12*]. Over a review period from 1960 to September 2010 we identified and obtained 146 full manuscripts, 133 were excluded due to multiple reasons. The remaining 13 studies were scored by an expert panel. Only three studies[13-15] with a total of 155 patients fulfilled all criteria for a diagnostic test accuracy studies[16-19]. These articles tested three different methods, pH measurement (64 patients)[13], insulin-like growth factor binding protein-1 (ILGBP-1, 83 patients)[14] and alpha fetoprotein (AFP, 8 patients)[15]. Sensitivity varied from 88% (pH) to 100% (AFP), specificity varied from 56% (ILGPP-1) to 100% (AFP). Based on the limited evidence on the accuracy of tests to diagnose ruptured membranes, we concluded that the use of a particular test cannot be recommended[12*].

For the present review, we repeated our search strategy for the period September 2010 until May 2012 and found 7 new articles, which will be described in more detail.

The lack of a gold standard

Amniocentesis with infusion of a dye is widely considered as the gold standard for the diagnosis of rupture of membranes. However, this procedure is invasive, costly and may itself cause rupture of membranes and other complications, such as infections[13,20-22]. Because of this, many researchers and medical ethical committees find it unethical to expose women to amnio-dye infusion. However over the last decades due to better ultrasound technology, success rate of amniocentesis improved and complication rate seems nowadays to be low[23]. Studies reporting adverse outcome were published between 1976 and 1983[20-22]. The last published study which used amnion infusion with a dye as a gold standard was performed more than 15 years ago. In that study, it took researchers 12 year to include 64 women[13]. Recently, preliminary results have been published in which placental alpha-microglobulin 1 (PAMG-1) was compared to amnio-dye test[24]. The final results have, however, not been published yet.
Meanwhile the lack of a noninvasive gold standard test for PROM is a severe limitation to study (new) diagnostic tests[25]. The recently published studies which are discussed in this review all lack the use of a gold standard and still do not meet all the criteria for the methodological assessment and reporting of diagnostic accuracy studies as suggested in previously reported guidelines[16-19].

Rationale of current diagnostic tests

Because of a lack of a gold standard for the majority of the clinical studies and the limitations and inaccuracy of “conventional testing” as well as the need for a less invasive, less intrusive method, researches have been searching for the identification biochemical markers which are present in high quantities in case of ROM, and absent in cervicovaginal discharge when membranes are intact. Many of these markers have shown to be less valuable because they are also present in other physiological fluid such as blood, vaginal secretion of seminal fluid[25]. Other markers such as fetal fibronectin (fFN) seem to indicate the mechanical or inflammatory-mediated detachment of the membranes from the decidua and are nowadays merely used as a predictor for pre-term delivery and are no longer considered to indicate ruptured membrane[26-28]. Insulin-like growth factor binding protein-1 (IGFBP-1) and placental alpha macroglobulin-1 (PAMG-1)meet the criteria of high concentration in amniotic fluid and low concentration in other physiological fluids[29,30]. Therefore in the past year the focus of the research has been on these two tests[31-36]. Other proteins, such as soluble intercellular adhesion molecule-1 (sICAM-1) and Axl receptor thyrosine kinase (Axl) might be used as biomarkers in the future[37*].

A bedside test to improve a doctor's confidence

Neil and Wallace[34] studied the clinical utility of PAMG-1 testing in daily practice. They questioned how often and in whom a bedside test might enhance the clinical diagnosis of PPROM and change clinical management. In a prospective observational study they included 184 women (100 term pregnancies and 84 preterm pregnancies) in a 12-month period. Based on history and clinical examination (speculum examination) the attending obstetrician was certain with the diagnosis in 53% of the women and uncertain in 47%. Obstetricians were more confident with preterm women than with term women (p=0.02). After PAMG-1 testing the confidence of the obstetrician in the diagnosis ROM or no ROM increased. In 92% of the women the obstetrician was certain with his/her diagnosis and in 8% uncertain (p<0.0001). Diagnosis and management was changed after PAMG-1 test especially in the proposed intact membranes group (toward proposed ruptured membranes, 14 out of 82 cases, 17%). The study did not test the accuracy of the PAMG-1 test, nor did it follow the women until delivery, not giving any insight in the effect on outcome. Results on the accuracy of PAMG-1 in this study should therefore be interpreted with caution. This study however does show the need for clinicians to increase his/her confidence by using a bedside test[34].

Diagnostic accuracy studies

Pollet-Villard et al., studied *in vitro* the sensitivity of IGFBP-1 and PAMG-1 using different detection limits after dilution of amniotic fluid in a comparative study[35*]. They recruited 41 women over 37 weeks of gestational age who were scheduled for a caesarean section. During the caesarean section 0.5 ml samples of amniotic fluid were collected with a syringe before rupture of the membranes and fetal extraction. The samples were diluted with saline solution (NaCl 0.9%) in a 1:10, 1:20, 1:40, 1:80, 1:160, 1:320 and 1:640 dilution series. For each dilution both IGFBP-1 and PAMG-1 tests were performed. Up to a dilution of 1:40 PAMG-1 showed a sensitivity of 100% whereas the sensitivity for IGFBP-1 dropped from 100 to 97.5% to 88% for 1:10, 1:20 and 1:40 dilution, respectively. For the dilution of 1:40 this difference was significant (p<0.05). This study tried to mimick the vaginal dilution of amniotic fluid in the vagina after PPROM. However, they only took samples for the term population and it might be questionable whether dilution with NaCl 0.9% will actually mimic the clinical condition. Nevertheless in this *in vitro* dilution study PAMG-1 has a higher sensitivity and better reproducibility than IGFBP-1[35*].

Two recent papers studied placental alpha microglobulin-1 (PAMG-1) for the detection of rupture of membranes[31,33]. The first study was a prospective observational study in 199 women (gestational age 17-42 weeks) with uncertain signs or symptoms of ROM[33]. Rupture of membranes was first diagnosed using a the conventional method with 2 out

of 3 of the following criteria: positive (1) visual leaking or pooling, (2) positive nitrizine test, (3) amniotic fluid index (AFI) <5 cm PAMG-1 testing was performed after initial diagnosis was made and the investigator was not blinded. Final diagnosis of ROM was made on medical records after delivery. PAMG-1 test was found to be more sensitive (94.4% vs. 72.2%, p=0.006) but had the same specificity (98.6% vs. 97.9%) compared to conventional testing. Due to the costs of ultrasound examination, PAMG-1 testing alone was significantly less expensive than conventional testing[33]. The second study was an unblended comparative prospective study in 150 term women (<37 weeks), 75 of whom had definite ROM, based on history (sudden gush), pooling, positive nitrazine and ferning and visual fluid passing the cervical canal during speculum examination, the remaining 75 women had no signs of ROM and were scheduled for induction of labour[31]. PAMG-1 testing in women with certain ROM had a sensitivity of 97% versus 84% for ferning and 87% for nitrazine test, specificity was 99%, 79% and 81% respectively[31].

Two other studies compared IGFBP-1 and PAMG-1 testing for diagnosis of ROM[32,36].

In the first prospective observational study 179 women between 16 and 41 weeks of gestation were included[32]. ROM was primarily diagnosed using a conventional method (pooling, positive ferning, positive nitrazine testing and AFI measurement). The definite diagnosis was made afterwards by two of the researches, unaware of the IGFPB-1 and PAMG-1 test result, based on duration of latency, results of (repeated) speculum examination, (repeated) ferning, nitrazine and decreased AFI by follow-up as well as clinical signs of fetal distress or chorioamnionitis. The presence of at least two of the above was needed for diagnosis of ROM[32]. The investigators found that the sensitivity (94%, 90%, 87%, for PAMG-1, ILGFBP-1 and conventional testing, respectively) and specificity (98%, 98% and 95%, respectively) were high and not statistically different. Related to ferning alone IGFBP-1 and PAMG-1 were significantly more accurate. However, as the researchers commented, ferning or nitrazine testing alone have been shown to be less accurate and are only used in a combined conventional method[32]. The second study compared ILGBP-1, PAMG-1 and nitrazine testing for diagnosing PROM. In a prospective observational study 100 consecutive women between 17 and 37 weeks of gestation with signs and symptoms of ROM were included. [36] ROM was diagnosed if three of the following were present: definite pooling, oligohydramion at ultrasound, signs and symptoms of chorioamnionitis, preterm delivery within a week of presentation along with a convincing history of leaking as judged by the attending clinician. Medical records were reviewed after delivery[36]. PAMG-1 had a sensitivity of 93% and specificity of 100%; IGFPB-1 had a sensistivity of 88% and specificity of 94%, the difference between both test was not statistically significant. Compared to nitrazine testing alone PAMG-1 and IGFPB-1 were significantly more accurate[36].

In another small observational study vaginal creatine was studied for diagnosing ROM in definite suspected- and absent ROM. It was concluded that vaginal creatine might be

useful in diagnosing ROM but material and methods of the study were poorly described, therefore no results are mentioned in this review[38].

Future testing methods

To date, PAMG-1 and IGFBP-1 are the most commonly used bedside test strips for diagnosing ROM. There is however some evidence that PAMG-1 might also be a marker for short time-to-delivery[39]. Fragmented and phosphorylated forms of IGFBP-1 are associated to predict preterm labour[40,41]. Like other diagnostic tests in the past, it might be possible that the sensitivity and specificity of PAMG-1 and IGFBP-1 will turn out to be not as high as reported to date.
Obviously, researchers are working on new tests which might be more accurate than currently available ones[37*]. Wang et al used a cytokine/chemokinine antibody array in order to identify proteins which are high in amniotic fluid (AF) and low in cervical-vaginal fluid (CVF) and tested these protein in 110 patients with unequivocal ROM and 110 controls[37*]. From the 174 cytokines which were studied in the kit, sICAM1, Axl, IGFBP-1, MCP-1, MIP-1δ, TIMP-1 and CD14 were found most interesting. The authors decided to focus on sICAM-1 (soluble intercellular adhesion molecule-1), Axl (Axl receptor tyrosine kinase) and IGFBP-1. sICAM, Axl and IGFBP-1 were respectively 85, 482 and 72 fold higher in AF than in CVF. sICAM and Axl maybe usefull as diagnostics for ROM where sICAM seems to be a better candidate for the development of a bedside test, because the technology to manufacture this test is widely accepted, reliable and inexpensive[37*].

Is there a need for a bedside test?

There is growing evidence that there is less need for immediate induction of labor when membranes rupture late prematurely[42,43]. This makes it questionable if for the near term population a bedside test is needed for a small minority of patients in which the clinician cannot certainly make a diagnosis based on conventional testing. However, in contrast early PPROM is associated with high perinatal morbidity and mortality. Preterm delivery is a frequent sequel of this complication and it is estimated that approximately 25-40% of preterm deliveries are preceded by PPROM. Although early preterm delivery (<32 weeks' gestation) occurs in only 1-2% of total births it is estimated to account for nearly 50% of all long-term neurological morbidity and about 60% of perinatal mortality[44].
In this perspective correct diagnosis in equivocal cases is mandatory since a correct diagnosis would bring down unnecessary burden for the health system. False positive test results could lead to overtreatment (hospital admittance, corticosteroids and

antibiotics), whilst a missed diagnosis of PPROM could delay administration of corticosteroids. In equivocal cases diagnosis of early PPROM is often hindered by vaginal bleeding. In a patient with mild vaginal bleeding in the second trimester the perspective in case of (masked) PPROM is significantly different, and a validated test in this case would be valuable.

Conclusion

Since we published a systematic review on the diagnostic tests for rupture of membranes[12*] several new studies have been published[31,32,34-38]. Due to the lack of a noninvasive gold standard, the use of a second best "silver standard" varies amongst different studies as well as the included population (preterm, term) and complaints (equivocal or unequivocal ROM). There were no randomised controlled trials, all studies were prospective and observational. Studies had small sample sizes (maximum 199 participants[33]) and therefore it is difficult to compare different tests with each other. PAMG-1 seems to be the most sensitive and specific test, and is subject of the only study with a design including the *real* gold standard dye-infusion results still being under way. New tests are being developed[37*]. But as long as current and newly developed tests are not tested against the gold standard, results of new studies will always be issue of debate. Furthermore in our opinion studies should be more focused on the early PROM group.

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Chapter 4

Is it useful to measure C-reactive protein and leukocytes in patients with prelabour rupture of membranes?

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Abstract

Neonatal infection is the main complication of prelabour rupture of membranes (PROM). We studied the accuracy of measuring C-reactive protein (CRP) and leukocytes in maternal serum to predict neonatal infection.

We performed a retrospective cohort study in two hospitals in the Netherlands between 2003 and 2006. We included consecutive women hospitalized for PROM. In both hospitals, CRP and leukocytes were measured routinely in maternal serum every 2 days until delivery. End points considered were clinical neonatal infection and proven neonatal sepsis. The accuracy of CRP and leukocytes was assessed using receiver operating characteristics (ROC) analysis.

We included 299 women with PROM, 12 of whom had a twin pregnancy. Gestational age at inclusion varied between 26 weeks and 0 days and 41 weeks and 5 days with a median of 37 weeks and 3 days. In 47 women (16%), the neonate developed a clinical infection. The areas under the ROC curve of CRP and leukocytes in the prediction of clinical neonatal infection were 0.61 and 0.62, respectively. Of the 47 infected neonates, six neonates (2%) had a proven neonatal sepsis. In the mothers of these septic neonates, maternal CRP did not rise above 50 mg/L and leukocyte values varied between 9.8 and 25.8 $x10^9$/l.

In women with PROM, CRP and leukocytes should not be measured routinely.

Introduction

Prelabour rupture of membranes (PROM) is defined as rupture of the membranes without the start of labour for at least 24 hours. The estimated incidence of PROM after 26 weeks of gestation is 10%[1]. The main complication of PROM is intrauterine infection. If the neonate is born immediately after PROM, the risk of sepsis is 2.5%, whereas it is thought to increase to 7.5% in cases of expectant management[2-4].
To determine the risk of neonatal infection before birth, several risk factors can be considered. Maternal fever, fetal tachycardia and green or fetid amniotic fluid are all associated with the presence of infection. Apart from these risk factors, it is thought that measuring C-reactive protein (CRP) and/or white blood cells (leukocytes) might be of value for early detection of neonatal infection in these patients[5,6].
In the literature, conflicting results on the use of CRP in the prediction of infection in women with PROM have been reported[5-7]. In 2007, Trochez-Martinez et al. performed a systematic review and found no clear evidence that supported the use of CRP for the early diagnosis of chorioamnionitis[8]. However, the association between CRP and neonatal infection was not assessed due to a lack of studies on the subject.
In view of this lack of knowledge, the objective of the present study was to determine the accuracy of CRP and leukocytes measured in maternal serum in the prediction of neonatal infection.

Methods

We performed a retrospective cohort study between 2003 and 2006 in the Orbis Medical Center Sittard and Máxima Medical Center Veldhoven. Both hospitals are large, nonacademic teaching hospitals in the south of the Netherlands. We included consecutive women with PROM, with a gestational age between 26 and 42 weeks. These women were identified from local electronic databases with data on all deliveries. In both hospitals, in women with PROM before 37 weeks' gestation, CRP and leukocytes were measured routinely in maternal serum twice a week until delivery. In women with PROM at term, CRP and leukocytes were measured 24 hours after rupture of the membranes and labour was induced after 48 hours. The measurements of CRP and leukocytes were used in combination with other data. The decision to induce labour or to continue expectant management (the probability of the presence of an intrauterine infection) was based on maternal fever, fetid or green amniotic fluid, tachycardia of the fetus, as well as on the results of CRP and leukocytes. In one of the hospitals (only in the Máxima Medical Center Veldhoven), antibiotics (erythromycin 250 mg 4 times daily for 10 days) were given to patients with PROM before 37 weeks' gestation[9]. The difference in this policy is a result of the guideline of the Dutch Society for Obstetrics and Gynecology, which does not give a clear recommendation on the use

of antibiotics in patients with PROM before 37 weeks' gestation. In both hospitals, patients with PROM before 34 weeks' gestation received intramuscular corticosteroid injections. Maternal CRP was measured with a turbidimetric immuno-assay (Roche Modular®, Basel, Switzerland). Leukocytes were measured with a flow cytometric test (impedance measurement from Beckman Coulter®, Brea, CA). Patients in whom CRP and leukocytes had not been measured were not included. For every patient with PROM, we collected data about the pregnancy, vaginal culture, maternal temperature, clinical infection in the neonate, admission to hospital and use of antibiotics in the neonate in a case record form.
End points were clinical neonatal infection and proven neonatal sepsis. According to the International Pediatric Sepsis Consensus Conference 2005[10], infection is suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) caused by any pathogen. Evidence of clinical infection includes symptoms with a high probability of infection, like positive findings on clinical exam, imaging, or laboratory tests. For signs of infection at clinical examination we used respiratory distress, tachypnea, lethargy (silent or hypotonic neonate), feeding problems, hyperthermia or hypothermia. Laboratory signs of infection were increased CRP, leukocytosis, or leukocytopenia[10].
Neonatal sepsis is defined as neonatal infection with cardiorespiratory instability or a positive blood culture caused by any pathogen.

Statistical analysis

The distribution of each of the variables was compared between the neonates with and neonates without infection. For continuous variables, we calculated means or medians in both groups. For statistical comparison, we used the appropriate statistical test depending on normality of the distributions.
Subsequently, for both CRP and leucocytes we performed receiver operating characteristic (ROC) analysis, in which infection was considered the disease. For comparison, the accuracy of maternal temperature for neonatal infection or sepsis was considered. The article was reported using the STARD-guidelines for the report of diagnostic research[11].

Results

We included 386 women with PROM, of whom 65 women were excluded, because CRP and leukocytes were not determined in these women. In 22 women, PROM had occurred before 26 weeks of gestation, leaving 299 women eligible for analysis (see Figure 4.1). Gestational age at inclusion varied from 26 weeks and 0 days to 41 weeks and 5 days with a median of 37 weeks and 3 days. Baseline characteristics are shown in

Table 4.1. In 47 women (16%), the neonate developed a clinical infection, of which six children (2%) had an early onset neonatal sepsis. The babies from the other 252 women did not develop an infection.

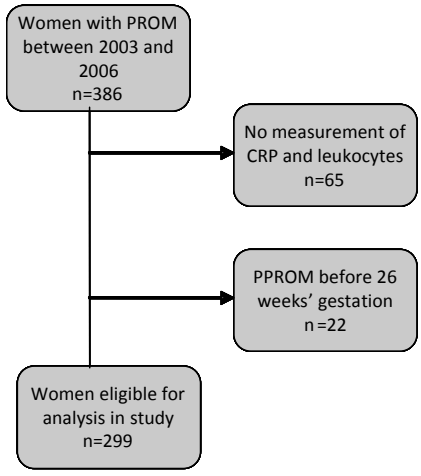

Figure 4.1 Inclusion of patients. CRP, C-reactive protein; PPROM, preterm prelabour rupture of membrane; PROM, prelabour rupture of membranes.

Table 4.1 Baseline characteristics.

Characteristic	Number	Number in women whose neonate had sepsis
Maternal age, y (mean and standard deviation)	30.4 years (±4.6)	28.3 years
Nulliparous women	196 (65.6%)	5 (83.3%)
Multiparous women	103 (34.4%)	1 (16.7%)
Gestational age (median and range)	37 wk, 3 d (26 wk-41 wk, 5 d)	36 wk, 2 d (31 wk, 1 d-40 wk, 4 d)
Singletons	287 (96.0%)	6 (100%)
Twins	12 (4.0%)	0 (0%)
Positive vaginal culture	123 (41.1%)	5 (83.3%)
Women who smoked	27 (9.0%)	1 (16.7%)

Values are expressed as absolute numbers with percentage, median with range or mean with standard deviation where appropriate.

In the 252 women with babies who did not develop infection, the last measured CRP in maternal serum before birth was minimum 1 mg/l and maximum 70 mg/l (median 8 mg/l) and the median leukocyte value was 13.0 (range 5.7 to 31.2 $x10^9$/l).
Of six children with early onset sepsis, one neonate suffered from *Listeria* meningitis and sepsis. Two children showed a hemolytic *Streptococcus* group B in the blood culture. One neonate had *Staphylococcus epidermidis* and one had *Staphylococcus*

capitis in the blood culture. One neonate had a neonatal infection and was hypothermic. The *S. epidermidis* in the blood culture might have been caused by contamination. However, this neonate also showed clinically signs of sepsis. In these six neonates with early onset sepsis, last measured CRP in maternal serum before birth did not rise above 50 mg/l and leukocyte values varied between 9.8 and 25.8 $x10^9$/l. We did not observe an effect of the use of antibiotics on the occurrence of sepsis.
In 47 women (16%), the neonate developed a clinical infection. The mean values of CRP, leukocytes and temperature in mothers of a child with clinical infection are shown in Table 4.2. Figures 4.2A and 4.2B show the ROC curves for CRP and leukocytes.
The area under the ROC curve for CRP and leukocytes in the diagnosis of clinical infection was 0.61 and 0.62, respectively.

Table 4.2 Clinical neonatal infection.

	Positive (*n*=47)	Negative (*n*=252)
C-reactive protein (mg/l)	21.7	11.7
Leukocytes ($x10^9$)	16.0	14.0
Maximal maternal temperature (°C)	37.2	36.8

Results are mean values.

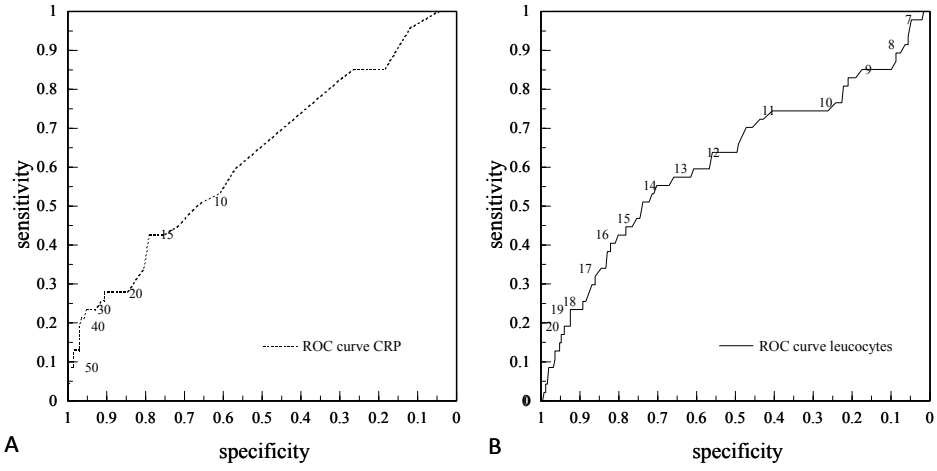

Figure 4.2 (A) Receiver operating characteristics (ROC) curve of C-reactive protein (CRP). Along the ROC curves, we have pointed the cutoff values. (B) ROC curve of leukocytes.

Figure 4.3 shows the ROC curve for the last maternal temperature measured before delivery in a similar plot as the curves for CRP and leukocytes. The area under the ROC curve was 0.61, and there was no clear clinical useful cutoff point for maternal temperature to diagnose neonatal sepsis.

Of the 299 included patients, 15 had a birth weight below the 10th percentile, of which three neonates had signs of infection. In these three neonates, maternal CRP values were 16 mg/l, 17 mg/l and 9 mg/l, respectively, whereas in the 12 low-birth-weight neonates without signs of infection, maternal CRP values varied from 3 mg/l to 27 mg/l. Thus, we did not find an indication that measuring CRP was useful in small-for-gestational-age infants.

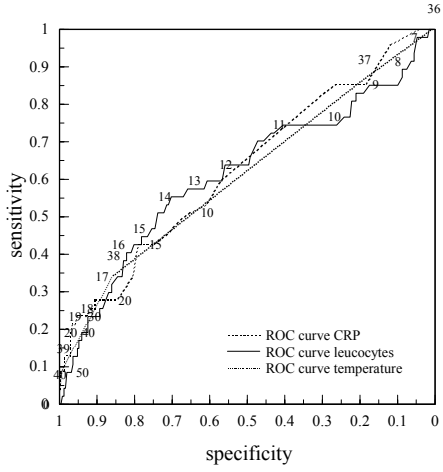

Figure 4.3 Combined receiver operating characteristic (ROC) curves of C-reactive protein (CRP), leukocytes and maternal temperature.

Discussion

We studied almost 300 women with PROM between 26 and 42 weeks' gestation. In the six children with early onset sepsis, maternal CRP last measured before birth did not rise above 50 mg/l and leukocyte values varied between 9.8 and 25.8 x10^9/l. CRP and leukocytes had an area under the ROC curve of only 0.61 and 0.62 in the prediction of clinical infection.

A possible limitation of this study is its retrospective character. In the study period, CRP and leukocytes might have been used in the decision to induce labour or to stop tocolysis. Although exact data on the number of patients in whom this occurred are not known, we do not think that this has a major impact on our results. Another limitation might be the subjectivity of the term "clinical infection". What some physicians might call a clinical infection might be interpreted as symptom(s) due to another cause by other physicians.

We tried to overcome this by making a list of possible symptoms of infection (e.g. tachypnea, feeding problems or hypothermia). If we could not find another explanation for these symptoms, we considered the symptom(s) as a clinical infection. Moreover,

the diagnosis of clinical infection was made independently from the results of CRP and leukocytes.

Among the 386 included patients, 56 did not have CRP and leukocytes measured. As this was a retrospective study, it is inevitable that some data are missing. It is possible that some patients had contractions and delivered before these parameters could be measured. These missing values occurred at random rather than systematically.

The fact that the results of CRP and leukocytes were known to the clinician might have caused bias. However, the complete absence of an association between CRP and leukocytes on one hand and the occurrence of sepsis on the other hand can not be explained completely by this bias.

As this was a retrospective study with limited resources, we did not perform a power calculation prior to our study, but rather decided to collect data over the period 2003 to 2006 as this was within our possibilities. Few studies on diagnostic accuracy report considerations of sample size[12]. A post hoc power calculation showed that the sample size of 47 cases with suspected infection was large enough to rule out with 95% certainty that the sensitivity of either CRP or leukocytes was higher than 64%. This is sufficient to conclude that the test is not useful in clinical practice. Similarly, the specificity was at maximum 56%.

Previous studies have reported the predictive capacity of CRP and leukocyte measurement in patients with PROM in respect to chorioamnionitis. Conflicting results were found, but overall CRP was shown not to be predictive for the early diagnosis of chorioamnionitis. Only Hirsch et al studied the association between CRP and neonatal infection and hypothesized that CRP might help determine the risk of infection, especially in infants with low birth weight[7].

At present, the effectiveness of induction of labour and expectant management in women with PPROM near term are evaluated in several multicenter trials[4,13]. In the PPROMEXIL trial, CRP and leukocytes in maternal serum are also measured. These data might provide new insight in the potential value of measuring CRP and leukocytes in maternal serum.

Because we found no evidence that measuring CRP and leukocytes in women with PROM is useful in the prediction of neonatal infection, we recommend that these parameters not be measured routinely these parameters in women with PROM. Particularly, these parameters should not be used to in the decision to induce labour or to maintain expectant management. Other factors, such as fetal tachycardia, fetid and/or green amniotic fluid, and maternal fever might be better indicators of intrauterine infection. Based on our study, we conclude that in women with PROM, CRP and white blood cells measured in maternal serum are poor predictors of neonatal infection. These parameters should therefore not be measured routinely in women with PROM.

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Chapter 5

The accuracy of clinical parameters in the prediction of perinatal pulmonary hypoplasia secondary to midtrimester prelabour rupture of fetal membranes: A meta-analysis

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Abstract

Prediction of pulmonary hypoplasia in women with midtrimester prelabour rupture of membranes (PPROM) is important for optimal management. We performed a systematic review to assess the capacity of clinical parameters to predict pulmonary hypoplasia. A systematic literature search in Embase and Medline was performed to identify articles published on pulmonary hypoplasia in relation to midtrimester PPROM. Articles were selected when they reported on one of the following clinical parameters - gestational age at PPROM, latency period and degree of oligohydramnios - , and when they allowed the construction of a two by two table comparing at least one of three clinical parameters to the occurrence of pulmonary hypoplasia. The selected studies were scored on methodological quality, and sensitivity and specificity of the tests in the prediction of pulmonary hypoplasia and lethal pulmonary hypoplasia were calculated. Overall performance was assessed by summary Receiver Operating Characteristic (sROC) curves that were constructed with bivariate meta-analysis. We detected 28 studies that reported on the prediction of pulmonary hypoplasia. Prediction of lethal pulmonary hypoplasia could be analysed separately in 21 of these studies. The quality of the included studies was poor. The estimated sROC curves showed that gestational age at PPROM performed significantly better than the two other parameters in the prediction of pulmonary hypoplasia. The accuracy in the prediction of lethal pulmonary hypoplasia was similar. In women with midtrimester PPROM, pulmonary hypoplasia can be predicted from the gestational age at PPROM. This information should be used in the management of women with early PPROM.

Introduction

Midtrimester prelabour rupture of membranes is associated with an increased risk of altered pulmonary development leading to pulmonary hypoplasia. In fetal lung development a critical interval, the canalicular phase, exists between 16 an 28 weeks gestation. Preterm prelabour rupture of membranes (PPROM) before 26 to 28 weeks can delay lung development and can cause pulmonary hypoplasia[1].

Pulmonary hypoplasia poses a serious threat due to its high mortality and morbidity rate. It can occur as severe respiratory failure leading to early neonatal death, as respiratory insufficiency with pulmonary haemorrhage, bronchopulmonary dysplasia, or subacute lung disease, or as mild and even transient respiratory disease[2]. Perinatal mortality approximates 70% in most series (55-100%)[3].

In a review of 11 studies on midtrimester PPROM, the reported incidence of pulmonary hypoplasia secondary to midtrimester PPROM ranged widely from 1 to 48%[4]. In another review the reported incidence also varied widely from 0 to 24%[1]. This wide range in prevalence is partly explained by the absence of uniform pathological and clinical definitions. Histological findings form the basis of the diagnosis, but autopsy is not always allowed or reported uniformly or informed consent is not obtained[2]. An international recognized definition of pulmonary hypoplasia does not exist, and it rather is a diagnosis par exclusionam[5]. Congenital pneumonia, Infant respiratory distress syndrome (IRDS) and pulmonary hypoplasia sometimes occur simultaneously, and have overlapping symptoms[1]. Moreover, there are methodological problems, such as differences in follow-up and lack of blinding.

Once midtrimester PPROM has occurred, an assessment of the probability of pulmonary hypoplasia is important both for clinical decision making and counselling of patients. Previous studies have shown that gestational age at the time of rupture of the membranes has a strong relation with the occurrence of pulmonary hypoplasia[6,7]. Other factors associated with pulmonary hypoplasia are the duration of the rupture of the membranes, and the degree of oligohydramnios[8]. To our knowledge, the predictive capacity of these clinical parameters for the presence of hypoplasia has not been assessed systematically. Therefore, we performed a meta-analysis on this subject. The aim of the present analysis was to assess the predictive capacity of clinical parameters in the prediction of pulmonary hypoplasia.

Materials and methods

We searched for studies that reported on neonatal outcome after midtrimester rupture of fetal membranes. We performed an electronic search of MEDLINE (Inception to 03/2008) and EMBASE (Inception to 03/2008), and checked reference lists of known

reviews and primary articles to identify cited articles not captured by electronic searches. There were no language restrictions.
To be included, studies had to fulfil the following criteria. The study had to report on the outcome of pregnancies complicated by PPROM between 14 and 28 weeks of gestational age.
Neonatal outcomes after midtrimester PPROM had to include the presence of pulmonary hypoplasia. The diagnosis of pulmonary hypoplasia could either be based on clinical and radiological findings or on findings at autopsy. In the analysis we distinguished two types of hypoplasia, i.e. lethal hypoplasia and any form of hypoplasia. Lethal hypoplasia was defined as hypoplasia resulting in the death of the fetus or neonate due to hypoplasia. Fetuses with autopsy proven lung hypoplasia after early pregnancy termination were also included in the lethal group. Any form of hypoplasia was defined as the sum of lethal hypoplasia and non-lethal hypoplasia. For each study, we calculated the prevalence of any form of pulmonary hypoplasia, and if possible of lethal pulmonary hypoplasia.
Studies also had to report on one of the three clinical parameters gestational age at PPROM, latency between PPROM and delivery, or oligohydramnios. The method by which oligohydramnios was defined was also documented, if applicable.
The following characteristics of each study were registered: (1) sampling (consecutive versus other), (2) data collection (prospective versus retrospective), (3) study design (cohort study versus case-control study), (4) blinding (present or absent), (5) verification bias and (6) selection bias[9]. Study characteristics were scored by two of the authors (*ASPvT* and *DvdH*). In case of disagreement, the judgement of a third author (*BWM*) was decisive.

Analysis

Data analysis

For each study, we constructed a two by two table cross-classifying one or more of the three clinical parameters and the presence of any form of pulmonary hypoplasia, and if possible, of lethal pulmonary hypoplasia separately. Two-by-two tables were constructed independently by two of the authors (*ASPvT* and *DvdH*). In case of disagreement, the judgement of a third author (*BWM*) was decisive.
To visualise data we plotted for each model combinations of sensitivity and specificity in Receiver Operating Characteristic (ROC) plots. A bivariate meta-regression model was used to calculate pooled estimates of sensitivity and specificity for risk score cut-off values and to fit a summary ROC (sROC) curve. This method has been extensively described elsewhere[10-13].
Briefly, rather than using a single outcome measure per study, like the diagnostic odds ratio, the bivariate model preserves the two-dimensional nature of diagnostic data in a single model. This model incorporates the correlation that may exist between

sensitivity and specificity within studies due to possible differences in threshold between studies. The bivariate model uses a random effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical or methodological differences between studies. In addition, the model acknowledges the difference in precision by which sensitivity and specificity have been measured in each study. This means that studies with a larger number of pregnancies resulting in pulmonary hypoplasia receive more weight in the calculation of the pooled estimate of sensitivity, while studies with more patients without hypoplasia are more influential in the pooling of specificity.
In case the sensitivity-specificity points were grouped alongside an imaginable underlying ROC-curve (i.e. studies with high sensitivity had relatively low specificity and vice versa), a sROC-curve was estimated, again using the bivariate model.
In case we looked at groups of studies that reported on the sensitivity-specificity points of multiple studies reporting on single cut-off value, for example a gestational age of 20 to 22 weeks, were grouped around an imaginable summary point-estimate, the pooled sensitivity and specificity were estimated with the bivariate model. This was done for gestational age below 18 weeks, 20 to 22 weeks, 23 to 24 weeks and above 25 weeks. For the latency period, i.e. the period between rupture of membranes and birth, we did so for more than 28 days, for more than 42 days and for more than 60 days. The way oligohydramnios was documented differed in the studies. Amniotic fluid index (AFI) – technique, according to Rutherford[14] has been used as well as the single deepest pocket (SDP) technique according to Chamberlain[15]. Also the amount nor the timing of measurements done throughout the latency period was uniform. Some authors used single measurements of amniotic fluid, whereas others used the mean or median of repeated measurements throughout the latency period. As our aim was to get a general impression on the prognostic accuracy of oligohydramnios, we considered any of the two definitions of oligohydramnios as abnormal test result.
The analysis was performed for the outcome ‘any form of pulmonary hypoplasia’. After this a separate analysis was done on studies that allowed construction of two by two tables on the outcome ‘lethal pulmonary hypoplasia’.
Finally, we compared the predictive capacity of all parameters with each other. The constructed sROC-curves for all parameters in the prediction of neonatal pulmonary hypoplasia were tested for statistical significant differences by entering the tests as co-variate in the bivariate regression model. A p-value of <0,05 was supposed to indicate a significant difference of one parameter as compared to the other.

Results

Figure 5.1 summarises the literature identification and selection process. For the three parameters “gestational age at time of rupture”, “latency” and “degree of

oligohydramnios", the computerised search detected 694 articles on pulmonary hypoplasia of which 108 were retrieved after reading the abstracts. After reading the full papers, eight articles were excluded since they did not contain original data, six articles were excluded since they did not report on the predefined study population, eight articles were excluded since they were therapeutical intervention studies, 28 articles were excluded since they did not report on the presence of pulmonary hypoplasia, and 30 studies were excluded since two by two tables could not be derived, leaving 28 articles that were available for analysis on any form of hypoplasia. From these 28 studies, 21 studies allowed construction of two by two tables on lethal pulmonary hypoplasia. There were 22 studies that reported on gestational age at PPROM, 13 that reported on latency, and nine that reported on oligohydramnios. The total number of pregnancies included in these studies was 1337. For the analysis on lethal hypoplasia the number of studies available was 19, 12 and five, respectively with in total 694 pregnancies.

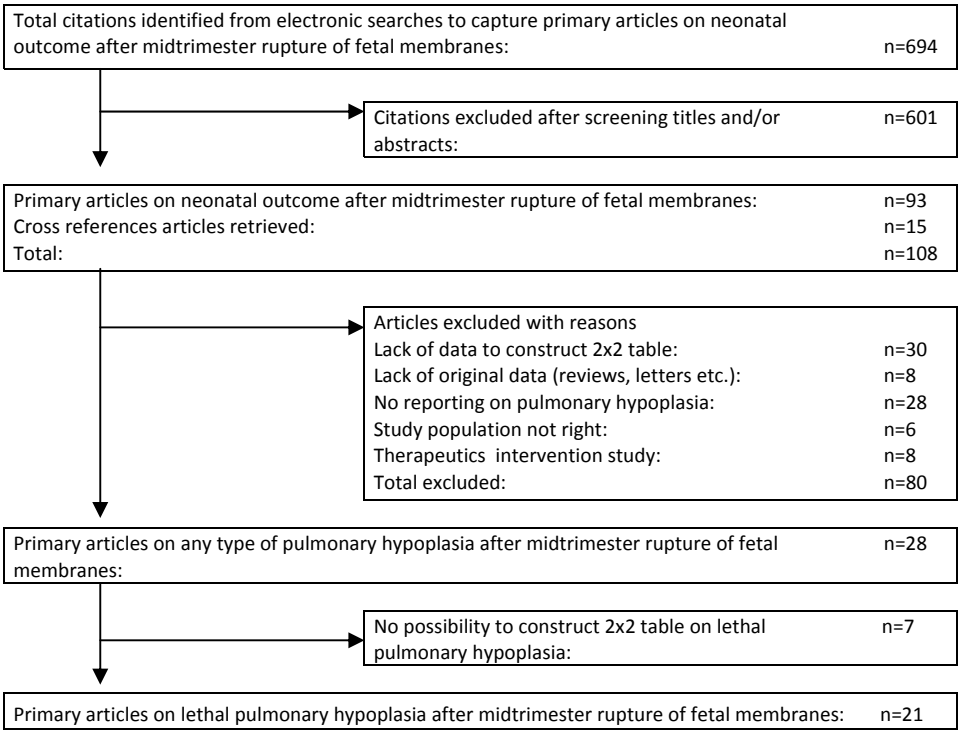

Figure 5.1 Process of literature identification and selection.

In three studies the upper limit of the range of the risk period extended beyond 28 weeks[17,27,37]. However, these studies were included since the large majority of patients was included at a gestational age below 28 weeks. Study characteristics of the 28 included studies are listed in Table 5.1. In 17 of the studies sampling of data was consecutive. Data collection was prospective in 18 studies, and 25 studies were designed as cohort studies. In only two studies blinding was performed. In the study of Laudy et al.[27] the radiologist was blinded to the sonographic measurements and the neonatal outcome, whereas in the study of Blott et al.[16] the doctors establishing the diagnosis were unaware of the ultrasound findings i.e. the amount of amniotic fluid. Selection bias was present in 20 studies and absent in five studies, whereas in three it was unclear whether this was present. Selection biases most frequently seen were exclusion of stillbirths, exclusion of terminated pregnancies, inclusion of fetuses with severe malformations, and limitation of studies to pregnancies with established oligohydramnios. Verification bias was present in 10 studies. Fourteen studies did not have verification bias whereas in four studies presence of verification bias was unclear. Study characteristics are summarized in Figure 5.2.

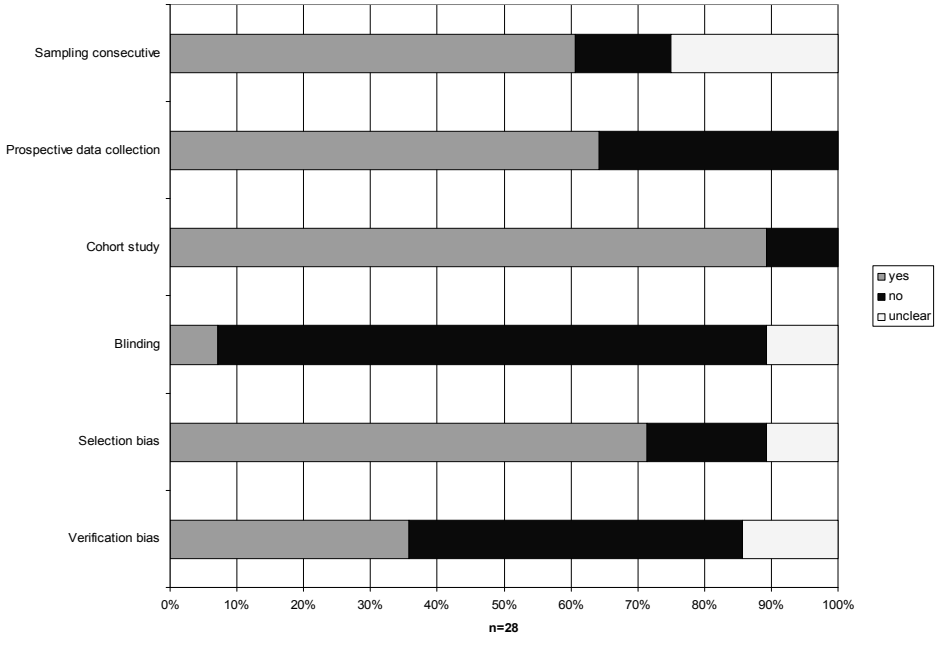

Figure 5.2 Study characteristics of the 28 detected studies.

Table 5.1 Patient characteristics.

Author	Year	n	Sub-group	Inclusion criteria	Exclusion criteria	Interval (wks)	Sampling consecutive	Data collection retrospective	Study design	Blinding	Selection bias	Verification bias	AFI or SDP
Blott[16]	1987	11		PPROM <30wks with oligohydramnios	Latency<48hrs,chorioamnionitis, malformations	15-26	Unclear	No	Cohort	Reference test: yes	Yes	No	
Blott[7]	1988	30		PPROM 15-28 wks	Latency<2wks	15-28	Yes	No	Cohort	Unclear	No	No	
Blott[17]	1990	20		PPROM <32wks with oligohydramnios	Latency<1wk	15-32	Unclear	No	Cohort	Unclear	Yes	No	
Carroll[18]	1995	172	82	PPROM resulting in live births, subgroup PPROM 16-28wks could be made	Multiple gestation	16-28	Yes	Yes	Cohort	Unclear	Yes	Yes	
Falk[19]	2004	57		PPROM 14-24 wks	PPROM <30 days after amniocentesis, cervical incompetence, latency <24 hours	14-24	Unclear	Yes	Cohort	No	Yes	Yes	
Farooqi[20]	1998	53		PPROM 14-28 wks	Multiple gestation, chorioamnionitis, latency <12 hrs	14-28	Yes	Yes	Cohort	No	Unclear	No	
Fong[21]	1988	13	9	PPROM 19-30, subgroup PPROM 19-27 wks could be made	Multiple gestation	19-27	Yes	No	Cohort	No	Yes	No	
Fortunato[22]	1994	24		PPROM <27 wks	Sealed rupture	15-27	Yes	No	Cohort	No	No	Unclear	SDP
Gerards[23]	2006	24	18	PPROM <34 wks with oligohydramnios, subgroup PPROM 16-26 wks could be made	Impossibility to perform us-measurements	16-26	Yes	No	Cohort	No	Yes	No	
Grisaru[4]	2003	25		PPROM <24 wks	Fetal malformations, chorioamnionitis	18-24	Yes	Yes	Cohort	No	Yes	No	
Hadi[24]	1994	178		PPROM 20-25wks	Fetal malformations, uterine leiomyoma, exposure to DES in utero, vaginal bleeding, placenta previa, incompetent cervix, multiple gestation.	20-26	Yes	No	Cohort	No	No	No	
Harstad[25]	1993	5		PPROM <22 wks, severe oligohydramnios		16-22	Unclear	No	Cohort	No	Yes	Yes	

Table 5.1 (continued)

Author	Year	n	Sub-group	Inclusion criteria	Exclusion criteria	Interval (wks)	Sampling consecutive	Data collection retrospective	Study design	Blinding	Selection bias	Verification bias	AFI or SDP
Kilbride[26]	1996	108		PPROM <29 wks, latency >3days	Multiple gestation, chorioamnionitis, fetal renal abnormalities	<29	Yes	No	Cohort	No	Yes	Yes	SDP
Laudy[27]	2002	42	31	Oligohydramnios as result of PPROM<30 wks,lasting>1wk, subgroup	Multiple gestation, fetal abnormalities	20-30	No	No	Cohort	Radiologist: Yes	Yes	No	SDP
Nimrod[28]	1984	100	30	PPROM >1 wk latency, subgroup <27wks made		10-27	Yes	Yes	Case control	No	Yes	Unclear	
Nourse[29]	1997	86	60	PPROM >12<26wks, >12hrs	Multiple gestation, letal malformations	13-26	Yes	Yes	Cohort	No	Yes	Yes	
Ogunyemi[30]	2002	12		PPROM <27 wks with oligohydramnios, subgroup of controls in intervention study	Clinical chorioamnionitis	18-28	No	No	Inter-vention study	No	Yes	Yes	
Ohlsson[31]	1991	23	15	PPROM <30wks, subgroup PPROM <28wks	Multiple gestation.	18-28	Unclear	No	Cohort	No	Unclear	Yes	AFI
Roberts[32]	1990	20		PPROM <25 wks		18-24	Unclear	No	Cohort	No	No	Yes	SDP
Rotschild[6]	1990	88		Neonates PPROM<29 wks, >1wk latency subgrp.	Major fetal abnormalities	15-28	Yes	Yes	Cohort	No	Yes	Unclear	
Shumway[33]	1999	118	100	PPROM 18-28 wks	Multiple gestation, fetal anomalies, chorioamnionitis, premature labour, abruption	24-28	Yes	No	Cohort	No	Yes	No	AFI
Sival[34]	1992	11	8	PPROM 19-29 wks, severe oligohydramnios AFI <1, subgroup PPROM <28wks	Latency <48hrs infection, PIH, IUGR, congenital malformations, Diabetes, use of sedatives, drugs or alcohol, fetal distress	19-28	No	No	Cohort	No	Yes	No	
Van Dongen[53]	1987	48	22	PPROM <34 wks, >1 wk latency	multiple gestation.	Ns-26	No	Yes	Case control	No	Yes	No	
Van Eyck[36]	1990	13		PPROM <28 wks, severe oligohydramnios, >3wks latency	Delivery <25 wks	16-27	Yes	No	Cohort	No	Yes	No	

Table 5.1 (continued)

Author	Year	n	Sub-group	Inclusion criteria	Exclusion criteria	Interval (wks)	Sampling consecutive	Data collection retrospective	Study design	Blinding	Selection bias	Verification bias	AFI or SDP
Vergani[37]	1994	63	54	PPROM <28 wks	Multiple gestation, PPROM after amniocentesis, congenital abnormalities, maternal immunocompromise	15-29	Yes	No	Cohort	No	Yes	Yes	SDP
Winn[38]	2000	163		PPROM 15-28 wks	Multiple gestation, fetal anomalies, chorioamnionitis , preexisting oligohydramnios	15-28	Unclear	No	Cohort	No	No	No	AFI
Xiao[39]	2000	28		Neonates PPROM <25 wks, born at <34 wks		14-24	Yes	Yes	Cohort	No	Yes	Unclear	
Yang[40]	2004	73		PPROM 16-26 wks	Multiple gestation.	16-26	Yes	Yes	Cohort	No	Unclear	Yes	

GA= gestational age, ROM = rupture of membranes, AFI= amniotic fluid index, SDP=single deepest pocket

The sensitivities and specificities for gestational age at PPROM, for latency between rupture membranes and date of birth, and for oligohydramnios in the prediction of any form of pulmonary hypoplasia are summarised in Table 5.2. A plot of sensitivity-specificity points and a sROC-curve for predictive capacities of gestational age at PPROM for any form of pulmonary hypoplasia is shown in Figure 5.3A. Two studies reporting on a gestational age at PPROM below 18 weeks showed a sensitivity of 62% and a specificity of 73%. For 20 to 22 weeks this was 70 and 73%, for 23 to 24 weeks this was 90 and 58%, whereas for cut-off values of 25 weeks and higher this was 96 and 48%, respectively.

Table 5.2 Results for any type of pulmonary hypoplasia.

Author	Number of babies with PH	n	Gestational age at rupture			Latency			Oligohydramnios (by AFI or SDP method)		
			cut-off in weeks	sensiti-vity	specifi-city	cut-off in days	sensiti-vity	specifi-city	cut-off in oligo-hydra-mnios	sensiti-vity	specifi-city
Blott '87	5	11	<20	0.60	0.50	>28	0.40	0.33			
			<27	1.00	0.00	>42	0.40	0.50			
						>70	0.20	0.83			
Blott '88	8	30	<16	0.38	1.00	>28	1.00	0.23			
			<18	0.63	0.73	>42	0.75	0.36			
			<20	0.88	0.68	>56	0.75	0.68			
			<22	1.00	0.59						
			<24	1.00	0.41						
Blott '90	5	20	<25	1.00	0.60						
Carroll	16	82	<20	0.56	0.88	>30	0.81	0.48			
			<24	1.00	0.45	>60	0.56	0.64			
			<28	1.00	0.00	>90	0.13	0.82			
						>120	0.00	0.96			
Falk	3	57	<20	1.00	0.67						
			<24	1.00	0.00						
Farooqi	9	53	<20	0.67	0.91	>28	1.00	0.77			
			<26	1.00	0.43	>42	0.89	0.64			
			<28	1.00	0.00	>56	0.67	0.93			
Fong	6	9	<22	0.50	0.67	>28	1.00	0.33			
			<27	1.00	0.00	>42	1.00	0.00			
						>56	0.67	1.00			
Fortunato	1	24							SDP≤1cm	1.00	0.70
Gerards	6	18	<20	0.33	0.58						
			<26	1.00	0.25						
Grisaru	3	25	<22	0.33	0.59						
			<24	1.00	0.00						
Hadi	2	178							SDP≤2cm	1.00	0.61
Harstad	2	5	<21	0.50	0.67	>28	0.50	0.33			
			<23	1.00	0.00	>56	0.50	0.33			
						>112	0.50	1.00			
Kilbride	23	108							SDP<1 cm	0.70	0.75
									SDP<2 cm	0.83	0.60

Table 5.2 (continued)

Author	Number of babies with PH	n	Gestational age at rupture			Latency			Oligohydramnios (by AFI or SDP method)		
			cut-off in weeks	sensiti-vity	specifi-city	cut-off in days	sensiti-vity	specifi-city	cut-off in oligo-hydra-mnios	sensiti-vity	specifi-city
Laudy	9	31	<20	0.78	0.77	>28	1.00	0.41	SDP≤1cm	0.78	0.82
			<24	1.00	0.45	>42	1.00	0.50	SDP≤2cm	1.00	0.32
			<26	1.00	0.32	>56	0.89	0.59			
Nimrod '84	8	30	<20	0.25	0.82						
			<26	1.00	0.00						
Nourse	10	60	<24	1.00	0.78						
			<27	1.00	0.00						
Ogunyemi	2	12	<22	0.50	0.70	>14	1.00	0.60			
			<25	1.00	0.10	>28	0.50	0.80			
			<28	1.00	0.00	>42	0.50	0.90			
Ohlsson '91	3	15	<22	1.00	0.92	>28	1.00	0.58	AFI<1cm	0.00	0.80
			<26	1.00	0.33	>42	1.00	0.75	AFI<5cm	1.00	0.25
						>56	0.00	0.83			
Roberts	12	20	<21	0.25	1.00	>28	0.42	0.75	SDP<1cm	0.75	1.00
			<23	0.75	0.87	>42	0.17	0.87	SDP<2cm	1.00	0.37
			<25	1.00	0.00	>56	0.17	0.87			
Rotschild	14	88	<20	0.36	0.96	>28	0.75	0.25			
			<22	0.50	0.92	>42	0.63	0.67			
			<24	0.57	0.84	>56	0.50	0.83			
Shumway	18	100							AFI<5cm	0.72	0.45
Sival	6	8	<22	0.17	1.00	>28	0.67	0.50			
			<24	0.67	0.50	>42	0.50	0.50			
			<26	1.00	0.00	>56	0.17	0.50			
VanDongen	4	22	<20	0.75	0.83						
			<26	1.00	0.00						
Van Eyck	5	13	<20	0.40	0.87	>42	1.00	0.37			
			<24	0.60	0.75	>56	0.40	0.75			
			<28	1.00	0.00						
Vergani	15	54							SDP<2 cm	1.00	0.38
Winn	21	163							AFI<1cm	0.52	0.74
Xiao	7	28	<22	0.71	0.71						
			<26	1.00	0.00						
Yang	8	73	<22	0.88	0.71						
			<26	1.00	0.00						

PH = Pulmonary hypoplasia; SDP = Single deepest pocket; AFI = Amniotic fluid index.

A plot of sensitivity-specificity points and a sROC-curve for predictive capacities of latency between rupture membranes and date of birth for any form pulmonary hypoplasia is shown in Figure 5.3B. Eleven studies reporting on a latency period of 28 days had a sensitivity of 85% and a specificity of 56%. For a latency period of 42 days this was 76 and 61%, for a latency period of 56 days this was 66 and 72%, whereas for a latency period of 60 days or higher this was 35 and 74%.

A plot of sensitivity-specificity points and a sROC-curve for predictive capacities of oligohydramnios for any form of pulmonary hypoplasia is shown in Figure 5.3C. Six studies reporting on oligohydramnios <1cm had a sensitivity of 60% and a specificity of 75%. For oligohydramnios <2cm this was 93 and 56%, respectively.

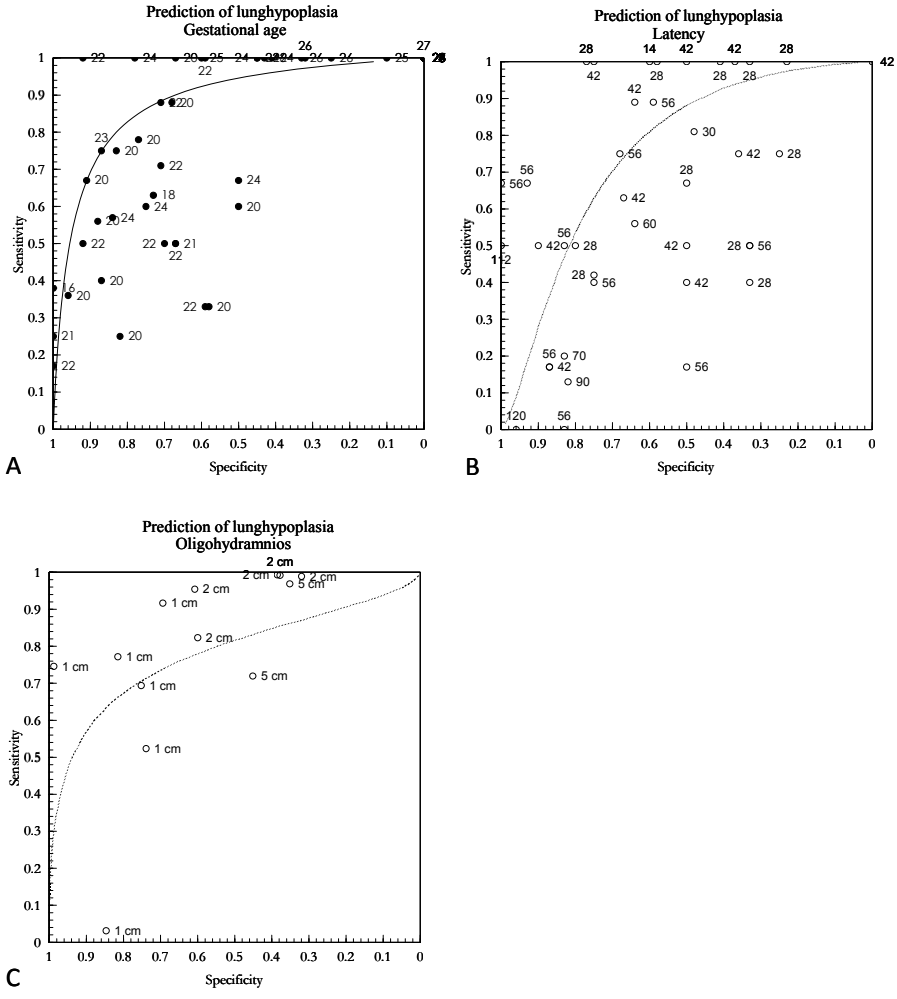

Figure 5.3 (A) Plot of sensitivity for 1 minus specificity - ROC plot for gestational age. Predictive capacities of gestational age at PPROM for any type of pulmonary hypoplasia. (B) Plot of sensitivity for 1 minus specificity - ROC plot for latency. Predictive capacities of latency between rupture membranes and date of birth for any type of pulmonary hypoplasia. (C) Plot of sensitivity for 1 minus specificity - ROC plot for oligohydramnion. Predictive capacities of oligohydramnion for any type of pulmonary hypoplasia.

Figure 5.4 shows the three sROC curves for the prediction of any form of pulmonary hypoplasia together. The sROC curve for gestational age at PPROM performed better than both latency and oligohydramnios. The differences between the predictive capacities of the three parameters were statistically significant, with P-values of 0.0041 (gestational age versus latency) and 0.0329 (gestational age versus oligohydramnios), respectively.
The sensitivities and specificities of gestational age at PPROM, of latency between rupture of membranes and date of birth, and of oligohydramnios for prediction of the lethal form of pulmonary hypoplasia are summarised in Table 5.3. Figure 5.4 also shows the three sROC curves for the prediction of the lethal form of pulmonary hypoplasia.

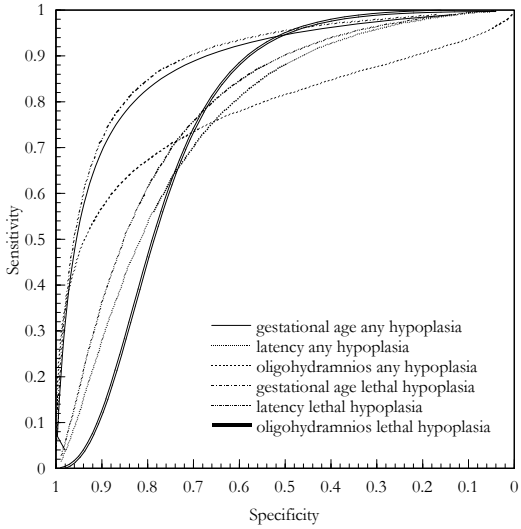

Figure 5.4 Receiver-operating-curve characteristic with the estimated summary ROC-curves for gestational age at PPROM, latency time and oligohydramnios for the prediction of lethal pulmonary hypoplasia and any hypoplasia.

Table 5.3 Results for lethal pulmonary hypoplasia.

Author	Number of babies with LPH	n	Gestational age at rupture			Latency			Oligohydramnios (by AFI or SDP method)		
			cut-off levels in weeks	sensiti-vity	specifi-city	cut-off levels in days	sensiti-vity	specifi-city	cut-off levels in oligo-hydra-mnios	sensiti-vity	specifi-city
Blott ' 87	5	11	<20	0,60	0,50	>28	0,40	0,67			
			<27	1,00	1,00	>42	0,40	0,50			
						>70	0,20	0,17			
Blott '88	8	30	<16	0,38	0,00	>28	1,00	0,77			
			<18	0,63	0,27	>42	0,75	0,64			
			<20	0,88	0,32	>56	0,75	0,32			
			<22	1,00	0,41						
			<24	1,00	0,59						
Blott '90	5	20	<25	1,00	0,40						
Carroll	16	82	<20	0,56	0,12	>30	0,81	0,52			
			<24	1,00	0,55	>60	0,56	0,36			
			<28	1,00	1,00	>90	0,13	0,18			
						>120	0,00	0,04			
Falk	3	57	<20	1,00	0,33						
			<24	1,00	1,00						
Farooqi	7	53	<20	0,86	0,09	>28	1,00	0,26			
			<26	1,00	0,59	>42	0,86	0,15			
			<28	1,00	1,00	>56	0,57	0,11			
Fong	4	9	<22	0,75	0,20	>28	1,00	0,80			
			<27	1,00	1,00	>42	1,00	0,40			
						>56	0,50	0,00			
Gerards	6	18	<20	0,33	0,42						
			<26	1,00	0,75						
Grisaru	3	25	<22	0,33	0,41						
			<24	1,00	1,00						
Harstad	2	5	<21	0,50	0,33	>28	0,50	0,67			
			<23	1,00	1,00	>56	0,50	0,67			
						>112	0,50	0,00			
Kilbride	23	108							SDP<1cm	0,70	0,25
									SDP<2cm	0,83	0,40
Laudy	9	31	<20	0,78	0,23	>28	1,00	0,59	SDP≤1cm	0,78	0,18
			<24	1,00	0,55	>42	1,00	0,50	SDP≤2cm	1,00	0,68
			<26	1,00	0,68	>56	0,89	0,41			
Ogunyemi	2	12	<22	0,50	0,30	>14	1,00	0,40			
			<25	1,00	0,90	>28	0,50	0,20			
			<28	1,00	1,00	>42	0,50	0,10			
Ohlsson '91	3	15	<22	1,00	0,08	>28	1,00	0,42	AFI<1cm	0,00	0,20
			<26	1,00	0,67	>42	1,00	0,25	AFI<5cm	1,00	0,75
						>56	0,00	0,17			
Roberts	12	20	<21	0,25	0,00	>28	0,42	0,25	SDP<1cm	0,75	0,00
			<23	0,75	0,13	>42	0,17	0,13	SDP<2cm	1,00	0,63
			<25	1,00	1,00	>56	0,17	0,13			

Table 5.3 (continued)

Author	Number of babies with LPH	n	Gestational age at rupture			Latency			Oligohydramnios (by AFI or SDP method)		
			cut-off levels in weeks	sensiti-vity	specifi-city	cut-off levels in days	sensiti-vity	specifi-city	cut-off levels in oligo-hydra-mnios	sensiti-vity	specifi-city
Sival	4	8	<22	0,00	0,25	>28	0,50	0,75			
			<24	0,50	0,75	>42	0,25	0,75			
			<26	1,00	1,00	>56	0,00	0,50			
VanDongen	4	22	<20	0,75	0,17						
			<26	1,00	1,00						
Van Eyck	4	13	<20	0,50	0,11	>42	0,75	0,56			
			<24	0,75	0,22	>56	0,50	0,22			
			<28	1,00	1,00						
Vergani	14	54							SDP<2 cm	1,00	0,63
Xiao	5	28	<22	1,00	0,26						
			<26	1,00	1,00						
Yang	5	73	<22	0,80	0,32						

LPH = Lethal pulmonary hypoplasia; SDP = Single deepest pocket; AFI = Amniotic fluid index.

Discussion

We included 28 studies that reported on the prediction of pulmonary hypoplasia in this review. Of these, 21 studies reported on lethal pulmonary hypoplasia specifically. The estimated sROC-curves showed that gestational age at PPROM performed significantly better than the two other parameters in the prediction of pulmonary hypoplasia. At a cut-off of 20 weeks, gestational age at PPROM had a sensitivity of 70% and a specificity of 73%. At a gestational age of 25 weeks, sensitivity and specificity were 96 and 48% respectively. The accuracy of gestational age at PPROM in the prediction of lethal pulmonary hypoplasia was similar. Most of the studies that we have identified have focussed on pulmonary hypoplasia without restriction to the lethal form. This is important, as accurate prediction of lethal pulmonary hypoplasia before 24 weeks gives parents the chance to opt for termination of pregnancy. Moreover, this information could be of clinical relevance in women in whom discussions on interventions have to be made at gestational ages around viability of the child. In case the gestational age is low, and the risk of hypoplasia is very high, the decision for a pointless caesarean section could be delayed. For non-lethal pulmonary hypoplasia this is less straight-forward, since termination of pregnancy is not justified as mild forms of pulmonary hypoplasia are also part of the clinical spectrum. Considering this, we aimed to assess the predictive capacities of the parameters in predicting pulmonary hypoplasia as well as lethal pulmonary hypoplasia.

The aim of this study was to assess the risk of *midtrimester* PPROM. The upper limit of the canalicular fase is thought to be a gradual limit with the outer boundary at 28 weeks[2]. Most studies on midtrimester PPROM have used 28 weeks as upper limit. Therefore, we chose 28 weeks as the upper limit of our inclusion interval rather than 26 weeks. However, we included three studies that exceeded the upper limit of the inclusion interval since the majority of patients in these studies was included at a gestational age below 28 weeks, and subgroups could not be made. The quality of the included studies was poor. This poor quality indicates that our estimates of sensitivity and specificity should not be considered as conclusive. However, we could not detect issues of poor quality that caused bias in a particular direction.

The assessment of oligohydramios varied in the frequency of measurements, the timing and the way they were defined (i.e. AFI or SDP). This makes definitive conclusions from this review on the role of oligohydramnios difficult. It has been suggested that spontaneous reaccumulation of amniotic fluid occurs in approximately 25% of cases of midtrimester PPROM[24]. Still, the presence of oligohydramnios on admission has been shown to correlate well with the average AFI[26,37,38].

The way midtrimester PPROM was managed varied per study. Administration of tocolytics,

antibiotics and steroids was not applied uniformly. These interventions might have influenced the latency period. Treatment at a neonatal intensive care unit can decrease mortality figures. The studies we included range from 1984 until 2008. Advance in neonatal high care could have resulted in lower mortality figures in more recent studies, with subsequently a lower incidence in lethal pulmonary hypoplasia.

The reference test used in the various articles has, unfortunately, shown a great deal of variations and can be a source of heterogeneity. Clinical diagnosis of pulmonary hypoplasia is difficult to establish[3]. Some studies have mentioned the presence of a certain number of cases of pulmonary hypoplasia retrospectively. This implies no initial intention to identifying these cases. Other studies have intended to look for cases with pulmonary hypoplasia but not every diseased neonate was performed autopsy on. These and other studies did sometimes also not look for clinical signs of pulmonary hypoplasia. Finally the technique to diagnose pulmonary hypoplasia in autopsy varies widely. Three criteria used to define pulmonary hypoplasia are the lung weight/body weight ratio, the radial alveolar counts and the amount of DNA detected in lung tissue. Each of these three criteria are having their own advantages and disadvantages[26,43]. All these factors account for a considerable verification bias. However, these are the only available data and thus they provide the best available evidence at present.

There is debate about the possible interaction of latency and gestational age at rupture[8,37,38,44]. Theoretically, the effect of latency on the occurrence of pulmonary hypoplasia could be influenced by the gestational age at PPROM, since it has been observed that early PPROM is related to longer latency. Also, it has been observed that a higher degree of oligohydramnios is associated with a shorter latency[37]. There

remains controversy on the role of latency on the occurrence of pulmonary hypoplasia. To our knowledge, at least two studies with larger sample sizes conclude that latency has an independent role[26,38]. Our review does not shed any more light on this issue.

It was shown that predictive capacities for lethal pulmonary hypoplasia and for pulmonary hypoplasia including the non-lethal form do not vary extensively. If the test is used in the decision for termination of pregnancy a positive predictive value close to 100% is required. This implies the need for a test (or combination of tests) with a very high (combined) specificity. Laudy[27] was able to reach 100% positive predictive value combining clinical, biometric and Doppler parameters with a sensitivity of 71%.

In conclusion, we found that gestational age at PPROM was a better predictor of pulmonary hypoplasia than latency and oligohydramnios. This is in line with the existing literature. The predictive capacities for pulmonary hypoplasia including the non-lethal form were similar. Obviously, better quality studies with larger samples on the issue are needed. In view of the low prevalence of midtrimester PPROM (0,7% of pregnancies), this requires studies performed in a multicenter setting. Uniform definitions of pulmonary hypoplasia are a prerequisite at the start of such studies.

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Chapter 6

Accuracy of imaging parameters in the prediction of lethal pulmonary hypoplasia secondary to mid-trimester prelabour rupture of fetal membranes: a systematic review and meta-analysis

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Abstract

In women who have suffered midtrimester prelabour rupture of membranes (PPROM) prediction of pulmonary hypoplasia is important for optimal management. We performed a systematic review to assess the capacity of imaging parameters to predict pulmonary hypoplasia. We searched articles that reported on biometrical parameters and allowed the construction of a two by two table comparing at least one of these parameters to the occurrence of pulmonary hypoplasia. The selected studies were scored on methodological quality, and we calculated sensitivity and specificity of the tests in the prediction of pulmonary hypoplasia and lethal pulmonary hypoplasia. Overall performance was assessed by summary Receiver Operating Characteristic (sROC) analyses that were performed with bivariate meta-analysis.

We detected 13 studies that reported on the prediction of lethal pulmonary hypoplasia. The quality of the included studies was poor to mediocre. The estimated sROC-curves for the chest circumference/abdominal circumference ratio and other parameters showed limited accuracy in the prediction of pulmonary hypoplasia.

In women with midtrimester PPROM, the available evidence indicates limited accuracy of biometric parameters in the prediction of pulmonary hypoplasia.

Introduction

In fetal lung development there is a critical interval, the canalicular phase, between 16 and 28 weeks' gestation. Preterm prelabour rupture of membranes (PPROM) before 28 weeks can delay lung development thus causing pulmonary hypoplasia[1]. Pulmonary hypoplasia poses a serious threat due to its high mortality and morbidity rate. It can occur as severe respiratory failure leading to early neonatal death, as respiratory insufficiency with pulmonary haemorrhage, bronchopulmonary dysplasia, or subacute lung disease, or as mild and even transient respiratory disease[2]. Perinatal mortality approximates 70% in most series (55-100%)[3].

Once midtrimester PPROM has occurred, assessment of the probability of pulmonary hypoplasia is important both for clinical decision making and counselling of patients. In a recent meta-analysis we assessed the predictive capacity of clinical parameters - gestational age at PPROM, latency period and degree of oligohydramnios for the presence of hypoplasia[4]. The gestational age at which PPROM occurred was a significantly better predictor than the latency period and degree of oligohydramnios for the occurrence of pulmonary hypoplasia. The accuracy in the prediction of the lethal variant of pulmonary hypoplasia was similar.

Biometric parameters assessed by ultrasound (two- or threedimensional, Doppler) or MRI have also been proposed as instruments to predict pulmonary hypoplasia following PPROM. To our knowledge, the predictive capacity of these parameters for the presence of hypoplasia after midtrimester PPROM specifically has not been assessed systematically. We therefore performed this meta-analysis to assess the capacity of biometric parameters assessed with ultrasound or MRI to predict pulmonary hypoplasia following mid-trimester PPROM.

Materials and methods

We searched the literature for studies that reported on neonatal outcome after mid-trimester PPROM, using combinations of the following search terms: pregnancy, oligohydramnios, fetal membranes – premature rupture, diagnostic imaging, fetal diseases, respiratory system,

fetal mortality, fetal death, infant mortality, pulmonary hypoplasia, lung hypoplasia, lung diseases and respiratory system. We performed an electronic search of MEDLINE (inception to 05-3-2011) and EMBASE (inception to 05-03-2011) and checked reference lists of known reviews and primary articles to identify cited articles not captured by electronic searches. Language restrictions were not applied.

The selection process was performed by one of the authors (A.S.P.v.T.). To be selected for inclusion, a study had to report on the outcome of pregnancies complicated by PPROM between 14 and 27 completed weeks of gestational age, in which any

ultrasound or MRI parameter was used with the goal of predicting pulmonary hypoplasia. The diagnosis of pulmonary hypoplasia could be based either on clinical and radiological findings or on findings at autopsy. For the purposes of analysis we distinguished two types of hypoplasia: lethal hypoplasia and any form of hypoplasia. Lethal hypoplasia was defined as hypoplasia resulting in the death of the fetus or neonate due to hypoplasia. Fetuses with lung hypoplasia proven on autopsy after early pregnancy termination were also included in the lethal group. Any form of hypoplasia was defined as the sum of all cases of hypoplasia, both lethal and non-lethal. We chose not to include cases of oligohydramnios caused by conditions other than mid-trimester PPROM, since these are other entities, with their own specific pathophysiology which might have influenced the outcome of our review. Moreover, the biometric indices studied in this review might have been influenced by these conditions, for example measurements in foetuses with polycystic kidneys or obstructive uropathy might be influenced by subsequent abdominal enlargement[5].

Studies had to report on any ultrasound or MRI parameter that was used with the goal of predicting pulmonary hypoplasia. The following characteristics of each study were noted: (1) sampling (consecutive or other), (2) data collection (prospective or retrospective) (3) study design (cohort study or case-control study), (4) blinding (present or absent), (5) verification bias (present or absent) and (6) selection bias (present or absent)[6].

Analysis

Data analysis

For each published study, its characteristics were scored by two of the authors (A.S.P.v.T. and J.v.d.H.), who each constructed independently a 2×2 table cross-classifying one or more of the imaging parameters with the presence of pulmonary hypoplasia. In case of disagreement, the judgement of a third author (B.W.J.M.) was decisive. It appeared that all but two studies found were aimed at diagnosing lethal rather than any form of pulmonary hypoplasia. Therefore, we limited the outcome in this review to lethal hypoplasia.

To visualize the data, for each model we combined sensitivity and specificity in the form of a receiver–operating characteristics (ROC) curve. A bivariate meta-regression model was used to calculate summary estimates of sensitivity and specificity for predictive values and to fit summary ROC (sROC) curves. The bivariate method has been described extensively elsewhere[7-10]. Briefly, rather than using a single outcome measure per study, such as the diagnostic odds ratio, the bivariate model preserves the two-dimensional nature of diagnostic data in a single model. This model incorporates the correlation that may exist between sensitivity and specificity within studies due to possible differences in threshold between studies. The bivariate model uses a random

effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical or methodological differences between studies. In addition, the model acknowledges the difference in precision by which sensitivity and specificity have been measured in each study. This means that studies with a larger number of pregnancies resulting in lethal pulmonary hypoplasia receive more weight in the calculation of the pooled estimate of sensitivity, while studies with more patients without hypoplasia are more influential in the pooling of specificity.
When individual study sensitivity–specificity points were grouped close to an imaginary underlying ROC curve (i.e. studies with high sensitivity had relatively low specificity and vice versa), an sROC-curve was drawn using parameter estimates from the bivariate model[11].
Differences in the capacity of all parameters to predict lethal pulmonary hypoplasia were tested for statistical significance by entering the tests as covariates in the bivariate regression model. $P<0.05$ was taken to indicate a significant difference of one parameter as compared with the other.

Results

Figure 6.1 summarizes the identification and selection process of the thirteen published studies included in this meta-analysis[12-24]. All studies reported on ultrasound parameters, and one also evaluated (two-dimensional) MRI parameters. Study characteristics of the 13 included studies are listed in Table 6.1. In two of the studies, sampling of data was consecutive. Data collection was prospective in all studies, and all studies were designed as cohort studies.

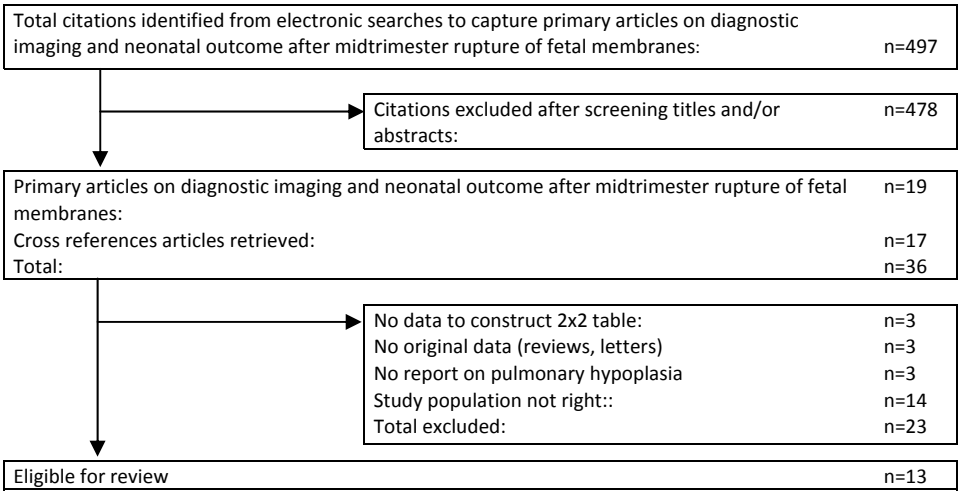

Figure 6.1 Process of literature identification and selection.

Table 6.1 Patient characteristics.

Author	Year	n	Sub-group	Inclusion criteria	Exclusion criteria	Interval (wks)	Sampling consecutive	Data collection retrospective	Study design	Blinding	Selection bias	Verification bias	Lph/ph
Blott[12]	1990	20	11 <24wks	PPROM <32wks with oligohydramnios	Latency<1wk	15-24	Unclear	No	Cohort	Radiologist: Yes	Yes	No	lph
d' Alton[13]	1992	16		PPROM <26 wks		15-26	Yes	No	Cohort	No	No	No	lph
Fong[14]	1988	12	11 <27wks	PPROM 19-30wks, subgroup <27wks could be made	Multiple gestation	19-27	Unclear	No	Cohort	No	Unclear	No	lph
Gerards[15]	2006	18		PPROM <34 wks with oligohydramnios, subgroup PPROM 16-28 wks could not be made	Impossibility to perform us-measurements	16-32	Unclear	No	Cohort	No	Yes	No	lph
Harstad[16]	1993	5		PPROM <22 wks, severe oligohydramnios		16-22	Unclear	No	Cohort	No	Yes	No	lph
Maeda[17]	1993	19	2	Cases at risk of developing lung hypoplasia, including two cases with PPROM at 22 wks		22	Unclear	No	Cohort	No	Yes	No	lph
Johnson[18]	1987	26	16 PPROM <28wks	PPROM <28wks >6days, Oligohydramnios>7 days with intact membranes		12-27	Unclear	No	Cohort	No	Unclear	No	ph, sens en spec for lph was calculated
Laudy[19]	2002	42	31	Oligohydramnios, subgroup as result of PPROM<30 wks,lasting>1wk, subgroup <28 could not be made	Multiple gestation, fetal abnormalities	20-30	No	No	Cohort	Clinicians and radiologist: Yes	Yes	No	lph
Nimrod[20]	1988	45		PPROM <30 wks (n=37), oligohydramnios <34 wks, pleural effusion or any condition potentially restricting lung growth, subgroup PPROM could <28 wks could not be made		<30	Unclear	No	Cohort	No	Yes	No	lph
Ohlsson[21]	1992	35		PPROM <30 wks, >5days, subgroup <28 weeks could not be made	No consent for autopsy	18-30	Unclear	No	Cohort	Yes, clinician and pathologist	Yes	No	lph

Table 6.1 (continued)

Author	Year	n	Sub-group	Inclusion criteria	Exclusion criteria	Interval (wks)	Sampling consecutive	Data collection retrospective	Study design	Blinding	Selection bias	Verification bias	Lph/ph
Rizzo[22]	1999	20		PPROM <24 wks, latency>2wks,s singleton, certain g.a., absence of fetal anomalies		18-23	Yes	No	Cohort	Investigator calculating PI blinded	No	No	lph
Roberts[23]	1990	20		PPROM <25 wks, >7 days		18-24	Unclear	No	Cohort	No	No	No	lph
Van Eyck[24]	1990	13		PPROM <28 wks, severe oligohydramnios, >3wks latency	Delivery <25 wks	16-27	Unclear	No	Cohort	Clinician: Yes	Yes	No	ph, sens en spec for lph was calculated

PPROM= premature prelabour rupture of membranes. PI=pulsatility index. LPH= lethal pulmonary hypoplasia. PH=pulmonary hypoplasia

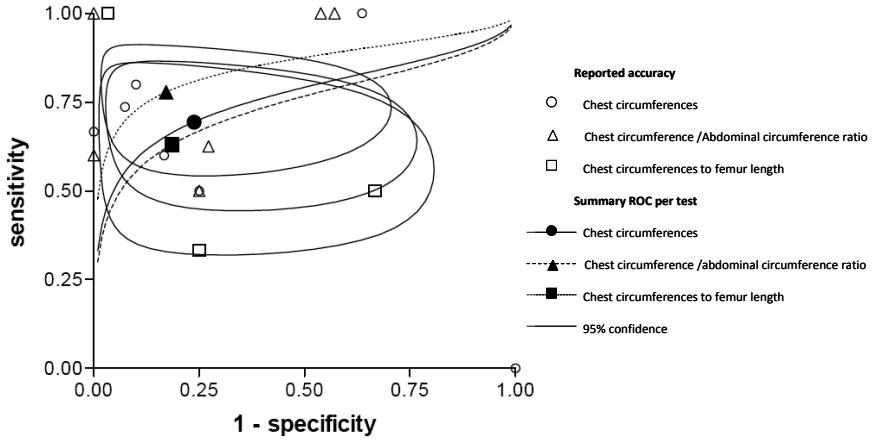

Figure 6.2 Sensitivity-specificity points and their reported accuracy for chest circumferences, the ratio of chest circumferences to abdominal circumferences, and for the ratio of chest circumferences to femur length for lethal pulmonary hypoplasia.

Five studies were adequately blinded. Selection bias was present in eight studies. Selection biases most frequently seen were limitation of studies to pregnancies with established oligohydramnios and inclusion of pregnancies in which PPROM occurred over 28 weeks. In one study of 45 pregnancies with oligohydramnios, in eight cases the oligohydramnios was not caused by PPROM[20]. Since in the majority of cases in this study the cause was PPROM, we included it in our review. One study excluded pregnancies in which measurements were unsuccessful or in which the results of reference tests were not obtained[15]. Verification bias was not present in any study. In six of the 13 studies, the diagnosis of lethal pulmonary hypoplasia was not always based on autopsy data; sometimes clinical and radiological data had to be used[14]. Table 6.2 gives characteristics of the biometric parameters that were used. The most commonly used ultrasound parameters were chest circumference (seven studies), chest circumference/abdominal circumference ratio (six studies) and chest circumference/femur length ratio (three studies). The MRI parameters used in the only study incorporating MRI were chest circumference and ratio of chest area minus cardiac area divided by cardiac area; volumes were not measured. The sensitivities and specificities for chest circumference, chest circumference/abdominal circumference ratio and chest circumference/femur length ratio, as well as some other parameters that were used less frequently in the diagnosis of lethal hypoplasia, are summarized in Tables 6.3 and 6.4, the former giving parameters derived from 2D ultrasound measurements, and the latter parameters derived from 3D ultrasound, 2D MRI or Doppler measurements.

Table 6.2 Test characteristics.

Author	Year	Parameter tested	2d US, 3d, Doppler, MRI	Timing of measurement	Definition / description of measurement	Exclusion because of unsuccesfull measurements	Normogram
Blott[12]	1990	ITC, LA	2d US	Measurement- delivery interval not stated.	ITC: internal thoracic circumference: a transverse section of the fetal thorax at the four chamber level of the heart during fetal apnoea, direct measurements of internal and cardiac (in diastole) circumferences . LA: Using these measurements the internal thoracic and cardiac areas were calculated assuming both areas to be circular, lung area was defined as the difference between the two areas.		Own reference range constructed of 76 normal pregnancies.
d' Alton[13]	1992	CC/AC	2d US	All pregnancies had an ultrasound within 2 weeks before delivery. Serial measurements, the last before delivery was used.	Thoracic circumference were performed in the transverse plane of the fetus at the level of the four chamber view of the heart, the fetal abdominal circumference was measured in the transverse plane at the level of the insertion of the umbilical vein.		Own standard curve created by measurements in 120 uncomplicated pregnancies.
Fong[14]	1988	CC/AC	2d US	Measurement within 5 weeks of delivery.	Abdominal circumference as described by Hadlock (AJR 1982). Chest circumference: a transverse section of the thorax was obtained at right angles to the fetal spine at the level of the atrioventricular valves, this section should be as round as possible and should contain the four chambers of the fetal heart.		Nomograms were constructed from measurements in 100 normal pregnancies
Gerards[15]	2006	TC/GA, TC/FL CC/AC, TA/HA 3DlvVSga, 3DlvVSefw	2d US, 3d US	Last measueremnt before delivery was used. For patients with lph mean interval measurement to delivery 2 1/7 week, without pulmonary hypoplasia 1 5/7th week.	AC, FL etc as described by Hadlock. The bony TC, HA and TA were determined from a cross section of the fetal thorax at the four-chamber view level, with the heart in ventricular diastole (Vintzileos, Ohlsson, Yoshimura and Laudy), TC/FL : cf Fong CC/AC cf Laudy, TA/HA cf Vintzileos: determined from a cross section of the fetal chest at right angles to the fetal spine at the level of the atrioventricular valves, with the heart in ventricular diastole. For 3D measurements: the free hand with positioning method was used. The upper and lower anatomical limits were respectively set at the level of the fetal clavicles and at the dome of the diaphragm in the transversal and sagittal plane. The outline of each lung was manually traced with 5-15 slices in 5-10 min. The volume of this 3D model was calculated by the software of the us machine and displayed in millilitres.	1 out of 24 excluded for impossible measurement (fetal positioning unfavourable.	3D: own reference curves (Gerards et.a. 2006). TC/FI/ Fong. TC/AC: Laudy et. al. 2002. TA/HA: Vintzileos et. al. 1989.

Table 6.2 (continued)

Author	Year	Parameter tested	2d US, 3d, Doppler, MRI	Timing of measurement	Definition / description of measurement	Exclusion because of unsuccesfull measurements	Normogram
Harstad[16]	1993	CC, CC/FL, (CA-HA)/CA	2d US, 2d MRI	US: the last was performed 0 to 5 weeks prior to delivery, at a mean of 2 weeks. MRI within 24 hrs of US	CC: cf nimrod, CC/FL cf Songster, (CA/HA)/CA cf Vintzileos: determined from a cross section of the fetal chest at right angles to the fetal spine at the level of the atrioventricular valves, with the heart in ventricular diastole. US and MRI measurements CC, (CA-HA)/CA, both in two dimensions. MRI measurements similar, however due to lack of freeze frame capability in MRI measurements not predictably obtained in diastole.		CC: cf nimrod, CC/FL cf Songster, (CA/HA)/CA cf Vintzileos.
Maeda[17]	1993	LA	2d US	Within 5 days of delivery.	Lung area was determined from a cross section of the fetal chest at right angles to the fetal spine at the level of the atrioventricular valves, with the heart in ventricular diastole. Lung area was determined as chest area minus heart area.		Own values (n=264) used for normogram
Johnson[18]	1987	TC/AC	2d US	Within 10 days of delivery.	The thoracic circumference was measured in the transverse plane of the fetus at the level of the four chamber view of the heart. Abdominal circumference was measured in the transverse plane of the fetus at the level of the stomach.		Callan et al 1984
Laudy[19]	2002	TC, CC/TC, TC/AC, doppler flow velocity parameters (PSV, PDV, EDV, TAV and PI)	2d US, doppler	The mean time between the measurements and delivery was 6 days.	Thoracic, cardiac, and abdominal circumference and the largest vertical amniotic fluid pocket were measured as described elsewhere (textbooks). This was followed by the pulsed doppler measurements of the arterial pulmonary branches from a transverse cross section of the fetal chest at the level of the cardiac 4 chamber view after visualisation with color doppler. Doppler waveformswere first obtained from the most proximal branch of the pulmonary artery, then in the middle lung region at equal distance from the from the outer border of the heart and the inner thoracic wall and subsequently in the distal lung region as close as possible tot the fetal inner thoracic wall.	2D parameters could be calculated in =>97%, Doppler parameters in 94, 84 and 68% respectively for proximal, middle and distal arterial pulmonary branch flow velocity waveforms	Own values previous patient cohort (111 uncomplicated singletons)
Nimrod[20]	1988	CC	2d US	Bi-weekly measurements until delivery, last measurement wa s used.	Cross section of the fetal chest at right angles to the fetal spine at the atrioventricular valves and demonstrating all chambers of the heart taken during episodes of absent fetal breathing.		Normogram by Nimrod 1986 from 83 normal pregnancies

Table 6.2 (continued)

Author	Year	Parameter tested	2d US, 3d, Doppler, MRI	Timing of measurement	Definition / description of measurement	Exclusion because of unsuccesfull measurements	Normogram
Ohlsson[21]	1992	CC/GA, CC/FL, CC/AC	2d US	Patients were studied at a time at which an US examination had been requested for clinical reasons.	A transverse section of the thorax was obtained at right angles to the fetal spine at the level of the atrioventricular valves.		Fong et al (1988)
Rizzo[22]	1999	Doppler (PI)	Doppler	Measurements repeated at weekly intervals until delivery.	The fetal chest was imaged in a transverse section at the level of the four chamber view of the heart. The sample volume of the pulsed Doppler was then placed in the most peripheral area of the fetal lung were vessels were evidenced. Velocity wave forms were recorded from PPA and vein.		Own normograms constructed from cross sectional study of 164 normal fetuses
Roberts[23]	1990	Lung Length	2d US	Weekly measurements, last measurement was used.	The length of the fetal lung was measured by taking a sagittal section through the fetal chest. The left lung was measured from the the tip of the apex to the base of the lung on the dome of the diaphragm during fetal apnea.		Normogram from 310 uncomplicated pregnancies.
Van Eyck[24]	1990	Doppler during fetal breathing (peak flow velocity modulation -delta PV)	Doppler during fetal breathing after iv glucose	Measurements nearest to delivery were considered, mean 3,8, range 0 to 7 days.	A longitudinal cross-section of the fetal ductus ateriosus was obtained on a short-view of the fetal heart parallel to the fetal spine as first described by Huhta et al.. The cursor was placed in the ductus near the junction of the ductus and the descending aorta. On the same view, fetal breathing can be observed, while doppler flow velocity measurements are performed. Measurements 30 minutes after intravenous glucose administration to the mother.	In one patient no doppler velocity measurements could be made during fetal breathing.	Normogram from 49 normal pregnancies.

US= ultrasound, ITC: internal thoracic circumference, LA= lung area, CC= chest circumference, AC= abdominal circumference, FL= femur length, GA= gestational age, US= ultrasound, 3D= three dimensional, TA= thoracic area, HA=heart area. 3DlvVSga= three dimensional lung volume versus gestational age, 3DlvVSefw= three dimensional lung volume versus estimated fetal weight. MRI=magnetic resonance imaging, CA=cardiac area. PSV=peak systolic velocity, PDV=peak diastolic velocity, EDV=end diastolic velocity, TAV=time-averaged velocity and PI=pulsatility index. PPA=peripheral pulmonary artery. PV=peak velocity. IV=intravenous.

Table 6.3 Results for lethal pulmonary hypoplasia, 2D ultrasound parameters.

Author	Nr. of babies with LPH	N	CC		CC/AC		CC/FL		Lung Area		Others, 2D US		
			Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Parameter	Sensitivity	Specificity
Blott[12]	5	11	0,60	0,83					0,60	0,67			
d' Alton[13]	6	16			1,00	1,00							
Fong[14]	4	12			1,00	0,50							
Gerards[15]	6	18	0,50	0,75	0,50	0,75	0,33	0,75			ta/ha	1,00	0,58
Harstad[16]	2	5	0,00	0,00			0,50	0,33			(ca-ha)/ca	0,50	0,33
Maeda[17]	1	2							1,00	1,00			
Johnson[18]	9	16			1,00	0,46							
Laudy[19]	9	31	1,00	0,36							cac/tc	0,78	0,50
	8	30			0,63	0,73							
Nimrod[20]	19	45	0,74	0,93									
Ohlsson[21]	5	35	0,80	0,90	0,60	1,00	1,00	0,97					
Roberts[23]	12	20	0,67	1,00							II	0,92	1,00

A plot of sensitivity–specificity points for chest circumference, chest circumference/abdominal circumference ratio and chest circumference/femur length ratio for lethal pulmonary hypoplasia is shown in Figure 6.2. The study of Laudy et al.[19] was the only one to report an optimal sensitivity for chest circumference, but this was at the expense of low specificity; the other six studies combined a high specificity with a sensitivity varying between 50% and 80%. The study of d'Alton et al.[13] was the only one to demonstrate perfect sensitivity and specificity for chest circumference/abdominal circumference ratio; all other studies had either suboptimal sensitivity or suboptimal specificity. Figure 6.3 shows the performance of chest circumference/abdominal circumference ratio, as in Figure 6.2, as compared with the sROC of our previous meta-analysis[4] which assessed the predictive capacity of gestational age at PPROM, latency time between PPROM and delivery and amount of amniotic fluid. The study of van Eyck et al.[24] used Doppler measurements during (induced) periods of fetal breathing. All these studies were relatively small, and none indicated that any of the evaluated tests had a good accuracy. The study of Ohlsson et al.[21] reported almost perfect accuracy for the chest circumference/femur length ratio, with a sensitivity of 100% and a specificity of 97%, but again the sample size in this study was rather low, as there were only 35 pregnancies in the cohort. Neither the amount nor the timing of measurements performed throughout the latency period was uniform, as can be seen from Table 6.2.

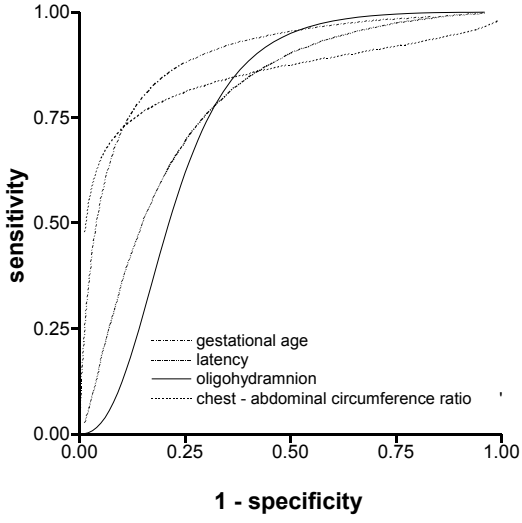

Figure 6.3 Performance of the ratio of chest circumferences to abdominal circumferences, as compared to the estimated summary ROC-curves for gestational age at PPROM, latency time and oligohydramnios for the prediction of lethal pulmonary hypoplasia.

Table 6.4 Results for lethal pulmonary hypoplasia, 3D ultrasound, 2D MRI, Doppler parameters.

Author	Nr. of babies with LPH	n	Parameter	Others	
				Sensitivity	Specificity
Gerards[15]	6	18	3D US lv/ga	0,83	1,00
			3D US lv/efw	0,67	1,00
Harstad[16]	2	3	2D MRI ca-ha/ca	0,00	1,00
			2D MRI cc	0,00	0,00
Laudy[19]	6	29	Doppler PPB tav	0,63	0,76
			Doppler PPB psv	0,63	0,9
			Doppler PPB pdv	0,25	0,9
			Doppler PPB edv	0,38	0,86
			Doppler PPB pi	0,38	0,76
	6	26	Doppler MPB tav	0,71	0,84
			Doppler MPB psv	0,43	0,84
			Doppler MPB pdv	0,14	0,68
			Doppler MPB edv	0,57	0,95
			Doppler MPB pi	0,29	0,79
Rizzo[22]	6	20	Doppler pi/ppa	0,63	0,95
Van Eyck[24]	4	12	Doppler during fetal breathing (peak flow velocity modulation - delta PV)	1,00	0,88

US=ultrasound, 3D=three dimensional, 2D=two dimensional, LA=lung area, CC=chest circumference, AC=abdominal circumference, FL=femur length, GA= gestational age, 3D=three dimensional, TA=thoracic area, HA=heart area. LL=lung length, CAC=cardiac circumference, TC=thoracic circumference lv=lung volume, efw=estimated fetal weight. MRI=magnetic resonance imaging, CA=cardiac area. PSV=peak systolic velocity, PDV=peak diastolic velocity, EDV=end diastolic velocity, TAV=time-averaged velocity and PI=pulsatility index. PPA=peripheral pulmonary artery. PV=peak velocity

Discussion

In this meta-analysis, we included 13 studies that reported on the prediction of lethal pulmonary hypoplasia. The estimates for sensitivity and specificity showed the capacity of imaging techniques to predict hypoplasia to be very limited. Our review identified several weaknesses in the literature. First, the methodological quality of the studies was limited. Many suffered from verification bias, as a result of the test being used in the management of the patients or because the observers were not blinded. All studies were single-center, which is worrisome, since second-trimester PPROM is a rare condition (0.7% of pregnancies), making it unlikely that a single-center study would reach sufficient power. Indeed, the sample size of each of the studies was rather small, especially with respect to the number of cases of hypoplasia. Most of the studies that we identified focussed on lethal pulmonary hypoplasia. This is important, as accurate prediction of lethal pulmonary hypoplasia before 24 weeks gives parents the chance to opt for termination of pregnancy. Moreover, this information could be of clinical relevance in women for whom discussions on intervention have to be made at

gestational ages around that of viability of the child. In women relatively early on in pregnancy who are at high risk of fetal lethal pulmonary hypoplasia, the decision for an unnecessary cesarean section could be delayed. As we included studies performed between 1988 and 2006, there will have been differences between them in terms of treatments. Differences in antenatal management (tocolysis, corticosteroids, antibiotics) and advances in neonatal intensive care could have resulted in lower mortality figures in the more recent studies, with a subsequent lower incidence of lethal pulmonary hypoplasia. The reference test used in the various articles showed strong variation, which is also a source of heterogeneity. In seven of the 13 studies, all cases with lethal pulmonary hypoplasia were proven by autopsy, albeit with different pathological standards. The technique to diagnose pulmonary hypoplasia in autopsy varies widely. The three criteria used to define pulmonary hypoplasia are lung weight/body weight ratio, radial alveolar count and amount of DNA detected in lung tissue (lung DNA (in mg)/body weight (in g) ratio). Each of these three criteria has its own disadvantage. (Wet) lung weight/body weight ratio is decreased in pulmonary hypoplasia; however, tissue edema could increase the ratio, confusing the diagnosis. Radial alveolar counts are difficult to interpret in the preterm lung before the development of alveoli. The numbers in a fixed expanded lung differ from those in a fixed collapsed lung. The lung DNA/body weight ratio is confounded by the presence of increased pulmonary interstitial inflammatory cells[25]. In six studies, some of the affected cases were identified by (predefined) clinical and radiological characteristics. However, a clinical diagnosis of pulmonary hypoplasia is difficult to establish since congenital pneumonia or infant respiratory distress syndrome sometimes occur simultaneously and have overlapping symptoms. The diagnostic meta-analysis we performed allows for control for heterogeneity in sensitivity and specificity, since both report on the same underlying test. When the cut-off for abnormality increases, sensitivity increases and specificity decreases, while a decrease in the cut-off for abnormality has the opposite effect. The summary ROC curves we estimated are a means of addressing this heterogeneity. We previously assessed the predictive capacity of gestational age at PPROM, latency time between PPROM and delivery and the amount of amniotic fluid[4]. Gestational age at PPROM performed significantly better than did the two other parameters in the prediction of pulmonary hypoplasia. Future studies should focus on whether ultrasound parameters or other imaging techniques can further improve on the prediction of pulmonary hypoplasia that is possible using age at PPROM. In view of the current evidence, we feel that there is no indication to perform such tests in a clinical setting.

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Chapter 7

Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks (Review)

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Cochrane Database Syst Rev 2013;8:CD009952

Abstract

Background
Preterm prelabour rupture of membranes (PPROM) before 26 weeks can delay lung development and can cause pulmonary hypoplasia, as a result of oligohydramnios. Restoring the amniotic fluid volume by transabdominal amnioinfusion might prevent abnormal lung development and might have a protective effect for neurological complications, fetal deformities and neonatal sepsis.

Objectives
To assess the effectiveness of transabdominal amnioinfusion in improving perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks.

Search methods
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013).

Selection criteria
All randomised controlled trials comparing transabdominal amnioinfusion with no transabdominal amnioinfusion. Cluster- or quasi-randomised trials were not eligible for inclusion. In cases where only an abstract was available, we attempted to find the full articles.

Data collection and analysis
Two review authors assessed trials for inclusion. No eligible trials were identified.

Main results
There are no included studies.

Authors' conclusions
There is currently no evidence to evaluate the use of transabdominal amnioinfusion in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks for improving perinatal outcome. Further research examining the effects of this intervention is needed. Two randomised controlled trials are ongoing but final data have not yet been published.

Summary

Babies born after preterm prelabour rupture of membranes (PPROM) between 16 and 26 weeks of pregnancy are prone to underdevelopment of the lungs. When the membranes containing the fluid that surrounds the baby (amniotic fluid) rupture, a shortage of this fluid can occur, a condition that is called oligohydramnios. Oligohydramnios is thought to interfere with normal lung development so that it is delayed, resulting in a condition that is called pulmonary hypoplasia.

Pulmonary hypoplasia can present as severe breathing problems or as milder and even transient breathing problems. It can be accompanied by bleeding in the lung and can also result in chronic breathing problems due to scarring of lung tissue. There may also be neurological complications, fetal deformities and neonatal sepsis with oligo-hydramnios.

Replacement of fluid via a needle passed through the abdominal wall in the uterine cavity and into a pocket of amniotic fluid, (transabdominal amnioinfusion) under ultrasound guidance has been proposed to improve pregnancy outcome. Most clinical experience suggests that amnioinfusion is safe for both the mother and the baby, however, we did not identify any randomised trials of transabdominal amnioinfusion following PPROM before 26 weeks for inclusion in this review. Currently, there is no evidence to evaluate the use of transabdominal amnioinfusion in women with oligohydramnios following rupture of fetal membranes before 26 weeks for improving birth outcomes.

Background

Description of the condition

It is thought that the formation of lung tissue is dependent on an adequate amount of amniotic fluid, especially during the interval between 16 and 26 weeks (the midtrimester). A reduced amount of amniotic fluid (oligohydramnios) after preterm prelabour rupture of membranes (PPROM) in this interval might cause pulmonary hypoplasia[1]. Oligohydramnios is commonly defined as a single deepest pocket of amniotic fluid of less than 2 cm or an amniotic fluid index of less than 5 cm as measured by ultrasound.

Pulmonary hypoplasia is a term used to describe pulmonary underdevelopment. It is characterised by an inadequate formation of the respiratory tree resulting in a reduced amount of functional lung tissue, with reduced capacity for gas exchange.

Pulmonary hypoplasia poses a serious threat to the neonate and is associated with high mortality and morbidity rates. It can present as severe breathing problems resulting in early neonatal death or, as milder and even transient breathing problems. It may be accompanied by bleeding in the lungs. It can also result in chronic breathing problems due to scarring of lung tissue[2]. Perinatal mortality approximates 70% in most series (55 to 100%)[3].

An internationally recognised definition of pulmonary hypoplasia does not exist, rather a diagnosis is made by eliminating other possible causes of symptoms. Congenital pneumonia, infant respiratory distress syndrome and pulmonary hypoplasia sometimes occur simultaneously, and have overlapping symptoms. Post mortem diagnosis is not uniform throughout the literature, however, post mortem criteria are more objective than those for infants who survive.

Apart from PPROM, numerous other conditions are associated with pulmonary hypoplasia. These include renal and urinary tract abnormalities leading to decreased amniotic fluid, decreased amniotic fluid unrelated to disorders of the urinary system, diaphragmatic hernia, fetal oedema, skeletal and muscular pathologies, central nervous system abnormalities, and other conditions causing compression of the fetal thorax[4].

Description of the intervention

Transabdominal amnioinfusion has been attempted for diagnostic and therapeutic purposes in women with second trimester oligohydramnios[5]. The aim of the procedure is to restore the amount of amniotic fluid, by infusing fluid through a needle passed through the abdominal wall into the womb. After sterile preparation of the abdomen, a pocket of amniotic fluid is identified by ultrasound guidance, after which a needle is advanced into this pocket. After insuring proper placement by withdrawing a small amount of fluid, the desired volume of fluid is infused, by manual push or infusion

pump. The procedure can be repeated if oligohydramnios recurs or persists (it is then called serial amnioinfusion).

How the intervention might work

The mechanism by which oligohydramnios impairs lung development is not fully understood. Several mechanisms have been proposed (mechanical effects, effects on fetal breathing movements, effects on the transcription of growth factors, and effects of inflammation and infection[6]. Restitution of amniotic fluid volume in cases of artificially induced oligohydramnios in experimental animals has prevented pulmonary hypoplasia[2,7].

Persistent oligohydramnios appears to be a poor prognostic sign in terms of pulmonary hypoplasia or other morbidity as described in a review by Laudy and Wladimiroff[3]. Restoring the amniotic fluid volume might prevent abnormal lung growth and development. Furthermore, it has been hypothesised that amnioinfusion might also have a protective effect for other neurological complications and fetal deformities[5]. Dilution, and the antibacterial effect of the infused fluid might have a protective effect for neonatal sepsis[8]. There is no consensus on the definition of successful amnioinfusion. Leakage of the infused fluid has been described. In two observational studies, in only 24% to 30% of cases was infused fluid retained 48 hours after the intervention[9,10].

Why it is important to do this review

In another Cochrane review Hofmeyr et al reviewed amnioinfusion for PPROM before 37 weeks with the aim to assess the effects of amnioinfusion for PPROM on perinatal and maternal morbidity and mortality[11]. Hofmeyr's review reports on transabdominal as well as transcervical amnioinfusion. It was concluded that transcervical amnioinfusion reduced variable decelerations during labour and improved fetal umbilical artery pH at delivery. Transabdominal amnioinfusion was associated with a reduction in neonatal death, neonatal sepsis, pulmonary hypoplasia and puerperal sepsis. Furthermore, the interval between PPROM and birth seemed to be longer in the amnioinfused group. It was stressed that the results should be interpreted with caution, since the positive findings were mainly due to one trial with unclear allocation concealment.

The present review, in contrast, specifically considers women with rupture of membranes before 26 weeks and subsequent oligohydramnios who are treated with transabdominal amnioinfusion.

PPROM before 26 weeks with oligohydramnios is a distinct condition within PPROM in general, with a distinct pathophysiology leading to abnormal lung development and a very poor prognosis. To date, no effective management has been recognised, although several therapies have been investigated. Some of these therapies aim to normalise the

amniotic fluid volume, either by preventing further leakage of amniotic fluid (occlusion by fibrin, platelets, cryoprecipitate), or to add fluid to the amniotic cavity by trans-abdominal amnioinfusion.

Antepartum amnioinfusion for the management of oligohydramnios is a difficult procedure. Technical difficulty lies in the fact that the needle has to be inserted in a pocket of amniotic fluid where, in severe oligohydramnios, such a pocket may be difficult to identify.
Some researchers have claimed that the procedure, if successful, has been shown to decrease the risk of pulmonary hypoplasia and significantly improves perinatal outcome[12].
Recently Porat et al.[13] reviewed transabdominal amnioinfusion for PPROM with associated oligohydramnios. Just as in Hofmeyr's review, studies on PPROM before 37 weeks were included. Porat 2012 meta-analysed available randomised controlled trials (RCTs) as well as observational studies. Two RCTs and one quasi-randomised RCT were included in the review as well as four observational studies. The two RCTs were carried out on women with PPROM between 24 and 34 completed weeks; the two RCTs were also included in the review by Hofmeyr[11]. The quasi-randomised study included only women with PPROM before 26 weeks of gestation[14]. Of the four observational studies, two were on very early PPROM. Porat et al. concluded that serial transabdominal amnioinfusion might improve early PPROM associated morbidity and mortality, however, a large randomised trial is needed.
A meta-analysis of all randomised controlled trials on women with PPROM before 26 weeks and associated oligohydramnios could indicate if serial transabdominal amnioinfusion is a safe and effective intervention for this specific obstetric problem.

Objectives

To assess the effectiveness of transabdominal amnioinfusion in improving perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Cluster- or quasi-randomised trials were not eligible for inclusion. In cases where only an abstract was available, we attempted to find the full articles.

Types of participants

Women with a pregnancy complicated by premature prelabour rupture of membranes (PPROM) before 26 weeks and subsequent oligohydramnios.

Types of interventions

Transabdominal amnioinfusion versus standard management.

Types of outcome measures

Primary outcomes

- Perinatal mortality, defined as intrauterine death, intrapartum death or neonatal death in the first 28 days of life.

Secondary outcomes

- Pulmonary hypoplasia as defined by the individual trials.
- Retention of infused fluid as defined by a single deepest pocket of amniotic fluid of more than 2 cm or an amniotic fluid index of more than five, for at least 48 hours.
- Gestational age at birth.
- Latency (interval between PPROM and birth).
- Neonatal mortality, defined as neonatal death in the first 28 days of life.
- Stillbirth (intrauterine death).

Neonatal morbidity

- Sepsis as defined by the individual trials.
- Respiratory distress syndrome as defined by the individual trials.
- Necrotising enterocolitis as defined by the individual trials.
- Chronic lung disease as defined by the individual trials.
- Periventricular leucomalacia as defined by the individual trials.
- Severe intraventricular haemorrhage as defined by the individual trials.
- Postural deformities as defined by the individual trials.

Adverse events

- Placental abruption.
- Cord prolapse.
- Chorioamnionitis as defined by the individual trials.
- Fetal trauma due to puncture.
- Premature labour and birth.
- Maternal sepsis as defined by the individual trials.
- Maternal death.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly search of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Stijn Van Teeffelen and Eva Pajkrt) independently assessed for inclusion all the potential studies that were identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted Ben Willem Mol (BWM).

There are no included studies. Data collection and analysis methods to be used in future updates of this review are provided in Appendix 1.

Results

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 11 reports. There are no included studies. We excluded nine studies[8,14-21] and two studies are ongoing[22,23].

Included studies

There are no included studies.

Excluded studies

We excluded nine studies from the review because they did not meet our study eligibility criteria (see Characteristics of excluded studies).
De Santis 2003 used a quasi-randomisation process in which women with PPROM before 26 weeks were allocated to amnioinfusion or expectant management, participants were admitted by chance into one of two departments, amnioinfusion was given in only one of these departments.
Gowri 2004 studied a group of 17 participants of which only three had premature rupture of membranes, data on their outcomes could not be extracted. Leake 1983 studied 35 participants with preterm labour and or ruptured membranes who received ritodrine or a placebo to study its effect on neonatal glucose homeostasis. Singla 2010 and Tranquilli 2005 were excluded since the inclusion criteria did not fit the criteria for this review (they studied participants with PPROM after 24 weeks) and Puertas 2007 and Nageotte 1985 studied intrapartum amnioinfusion in women with PPROM between 26 and 35 weeks. We excluded Gonzalez 2001 since we could not find the final data published (preliminary results). The Vergani 2007 report is a study proposal.

Risk of bias in included studies

There are no included studies.

Effects of interventions

There are no included studies.

Discussion

No randomised controlled trials of transabdominal amnioinfusion to improve perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks were identified for inclusion in this review. Two randomised controlled trials have started[22,23] but final data have not yet been published.
At this point, transabdominal amnioinfusion cannot be recommended for women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks. Women requesting a trial of therapy should be informed of the lack of any well-designed studies assessing effectiveness, and the risk of adverse events.

Authors' conclusions

Implications for practice

There is currently no evidence to evaluate the use of transabdominal amnioinfusion for improving perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks.

Implications for research

Randomised controlled studies to determine the effectiveness of transabdominal amnioinfusion in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks are needed.

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Chapter 8

Midtrimester preterm prelabour rupture of membranes (PPROM). Expectant management or Amnioinfusion for improving perinatal outcomes (PPROMEXIL – III trial)

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Accepted subject to revision

Abstract

Background
Babies born after midtrimester preterm prelabour rupture of membranes (PPROM) are at risk to develop neonatal pulmonary hypoplasia. Perinatal mortality and morbidity after this complication is high. Oligohydramnios in the midtrimester following PPROM is considered to cause a delay in lung development. Repeated transabdominal amnioinfusion with the objective to alleviate oligohydramnios might prevent this complication and might improve neonatal outcome.

Methods/Design
Women with PPROM and persisting oligohydramnios between 16 and 24 weeks gestational age will be asked to participate in a multi-centre randomised controlled trial. Intervention: random allocation to (repeated) abdominal amnioinfusion (intervention) or expectant management (control). The primary outcome is perinatal mortality. Secondary outcomes are lethal pulmonary hypoplasia, non-lethal pulmonary hypoplasia, survival till discharge from NICU, neonatal mortality, chronic lung disease (CLD), number of days ventilatory support, necrotizing enterocolitis (NEC), periventricular leucomalacia (PVL) more than grade I, severe intraventricular hemorrhage (IVH) more than grade II, proven neonatal sepsis, gestational age at delivery, time to delivery, indication for delivery, successful amnioinfusion, placental abruption, cord prolapse, chorioamnionitis, fetal trauma due to puncture. The study will be evaluated according to intention to treat. To show a decrease in perinatal mortality from 70% to 35%, we need to randomise two groups of 28 women (two sided test, ß-error 0.2 and α-error 0.05).

Discussion
This study will answer the question if (repeated) abdominal amnioinfusion after midtrimester PPROM with associated oligohydramnios improves perinatal survival and prevents pulmonary hypoplasia and other neonatal morbidities. Moreover, it will assess the risks associated with this procedure.

Background

Preterm prelabour rupture of membranes (PPROM) before or near the limit of viability is associated with high perinatal morbidity and mortality. Respiratory complications are frequent after periviable PPROM, as well as sepsis, intraventricular haemorrhage, retinopathy and necrotising enterocolitis (NEC). Among respiratory complications pulmonary hypoplasia is an important cause of death. Other respiratory complications consist of pneumonia, Infant respiratory distress syndrome (IRDS) and broncho-pulmonary dysplasia (BPD).

PPROM before 26 weeks can delay lung development and can cause pulmonary hypoplasia [1]. Pulmonary hypoplasia is a term to describe an altered pulmonary development characterised by a reduction in the number of pulmonary alveoli or in bronchial branching. In fetal lung development a critical interval, the canalicular phase, exists between 16 and 28 weeks gestation. Gestational age at rupture of membranes has been shown to be inversely related to the risk of pulmonary hypoplasia.

Pulmonary hypoplasia results in severe respiratory failure leading to early neonatal death, respiratory insufficiency with pulmonary haemorrhage, bronchopulmonary dysplasia, or sub-acute lung disease, or sometimes in mild transient respiratory disease[2]. Perinatal mortality approximates 70% in most series (55-100%)[3].

In a review of 11 studies on midtrimester PPROM, the reported incidence of pulmonary hypoplasia secondary to midtrimester PPROM ranged widely from 1% to 48%[4]. A review of 6 studies on PPROM before 24 weeks reported an incidence of pulmonary hypoplasia of 19% (n=120)[5]. These percentages do not represent the true natural history, given the limitations of these reviews, summarising only retrospective cohorts from tertiary care centres. The wide range in prevalence is partly explained by the absence of uniform pathological and clinical definitions. Histological findings form the basis of the diagnosis pulmonary hypoplasia, however complete autopsy data were often not available[2]. An international recognized definition of pulmonary hypoplasia is lacking, and it rather is a diagnosis by exclusion[6]. Congenital pneumonia, infant respiratory distress syndrome (IRDS) and pulmonary hypoplasia sometimes occur simultaneously, and have overlapping symptoms[1]. Moreover, there were metho-dological problems in the reviews, such as differences in follow-up and lack of blinded assessment of the endpoints.

Pregnancies complicated by midtrimester PPROM are associated with high immediate and long-term costs. These are caused by extended maternal hospital admissions, increased incidence of premature delivery, and frequent neonatal complications hereafter requiring NICU-admission.

Amnioinfusion might improve fetal outcome by preventing pulmonary hypoplasia, by preventing neurological complications, increasing time to delivery interval, and improving fetal biophysical profile through prevention of umbilical cord compression. It also might prevent fetal deformity[7]. Porat et al.[8] reviewed serial transabdominal

amnioinfusion and meta-analysed observational as wel as randomised studies. The only two included randomised studies however were on women with PPROM between 24 and 34 weeks whereas the critical interval for development of pulmonary hypoplasia, the canalicular phase, exists between 16 and 28 weeks gestation. One quasi-randomised study included women with PPROM before 24 weeks. There were two observational studies on PPROM before 24 weeks. Recently, Roberts et al.[9] published the only randomized trial on PPROM between 16 and 24 weeks. They found no difference in the primary outcome (perinatal mortality 19/28 vs. 19/28; RR 1.0; 95% CI0.70-1.43), maternal or neonatal morbidity. The observed difference in long term outcome (4/28 morbidity free survival at 2 years in the treatment group vs. 0/28 in the group with expectant management) justifies further study.

Adverse events after antepartum transabdominal amnioinfusion have been reported. It is not clear which adverse effects are to be attributed to the procedure rather than to the condition of PPROM and oligohydramnios, since conservatively managed PPROM carries high risks inherent to the condition itself[7]. Waters and Mercer recently reviewed perinatal mortality after conservatively managed PPROM <26 weeks[5]. Meta-analysis of 6 studies (n=275) shows a perinatal mortality of 54%, (if restricted to <24 weeks this incidence is 57%). These data are biased by the fact that patients not amenable to continued expectant management were often excluded (i.e. stillbirths, pregnancy terminations), and therefore survival is likely to be overestimated.

A retrospective analysis by Van der Heijden et al. on outcome after PPROM in three tertiary centres in The Netherlands was recently published[10]. Their study included 14 multiple pregnancies. When these were excluded, in 164 singleton pregnancies with PROM before 24 weeks there was a perinatal mortality of 71%. Of all mortality 38% occurred in the neonatal period (data not published). It can be questioned whether all pregnancies with PROM <24 weeks have been referred. Lethal pulmonary hypoplasia was documented in only 16 cases (10%), which is probably an underestimation as discussed before (personal communication by Van der Heijden).

In summary, midtrimester PPROM is associated with a high incidence of perinatal mortality, pulmonary hypoplasia and other neonatal complications. Exact incidences are difficult to obtain because of selection biases, probably leading to substantial underreporting. Diagnosis of pulmonary hypoplasia is difficult due to overlapping symptoms and absence of uniform definitions. Amnioinfusion might be beneficial, however there is no solid evidence to incorporate this seemingly safe procedure in daily practice. Therefore we believe there is the need to assess the role of amnioinfusion after midtrimester PPROM. We are currently conducting a multicentre randomised controlled clinical trial. This study is conducted within the Dutch Obstetric Consortium, a collaborative effort of obstetric clinics in The Netherlands to perform clinical trials. Seven Dutch perinatal centres with NICU facilities participate in this trial.

Methods and design

Aims

The primary aim of this study is to evaluate the effectiveness of amnioinfusion compared to expectant management for relieving oligohydramnios in women with midtrimester PPROM occurring before 24 weeks gestational age in reducing perinatal mortality and neonatal morbidities.

Participants/eligibility criteria

All women with a singleton pregnancy who are first diagnosed between 16 and 24 weeks gestational age with oligohydramnios secondary to PPROM, at least 72 hours after PPROM was diagnosed, but no longer than 21 days after the diagnosis of oligohydramnios, are eligible for the trial. Women with oligohydramnios secondary to iatrogenic PPROM are also eligible.
We will exclude women with signs of uterine contractions, (8 uterine contractions per hour) intrauterine infection (temperature >38°C plus fetal tachycardia or uterine tenderness or foul/purulent amniotic fluid), a pregnancy complication (hypertension, HELLP syndrome, preeclampsia or other) in which there is a need for termination of pregnancy, placental or major structural fetal anomalies, signs of cervical incompetence (visible cervical dilatation or a cervical length of <25 mm), and women whose child has signs of fetal distress (abnormal biophysical profile).

Procedures, recruitment, randomisation and collection of data

The research nurse and/or the staff of participating hospitals will identify eligible women. Prior to randomisation, in all patients amniotic fluid loss will be objectified by sterile speculum examination for visible fluid loss from the cervical os, by a nitrazine- and/or ferning test. Speculum examination will be performed to exclude signs of cervical incompetence (visible dilatation). Hereafter patients will undergo an ultrasound examination to determine the single deepest pocket (SDP) of amniotic fluid and to exclude placental and or fetal structural anomalies. At this time ultrasound measurements used in the prediction of pulmonary hypoplasia - TC/AC (thoracic circumference/ abdominal circumference), TC/FL (thoracic circumference/ femur length), Doppler measurement of pulmonary artery proximal branch peak systolic velocity, 3D lung volume measurement -, will be performed by specialized personnel.
If oligohydramnios is present (SDP<2cm) patients will be counselled for the study. Randomisation, will take place immediately after informed consent has been obtained, at least 72 hours after diagnosis of PPROM. See also Figure 8.1.

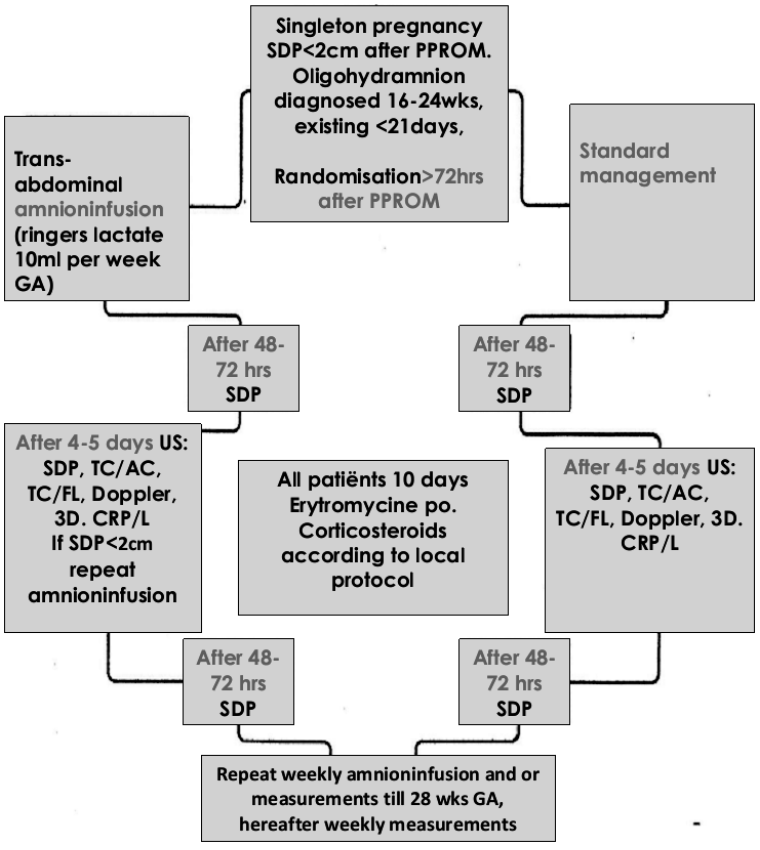

Figure 8.1 Flowchart PPROMEXIL-III trial.

Randomisation will be performed, using an internet-based procedure, with the use of a permuted-block design, after informed consent and baseline data have been entered in a web-based database system.

Treatment allocation will obviously have to be unblinded for patients and clinicians and sonographers, and the personnel performing the ultrasound investigations, however, allocation will remain blinded for paediatricians, pathologists and/or radiologists who are assessing outcomes.

All data are collected, coded and processed with adequate precautions to ensure patient confidentiality. The investigators will publish the results of the study in a peer reviewed medical journal as soon as appropriate.

Interventions

The intervention being evaluated is trans-abdominal amnioinfusion. After sterile preparation of the abdomen, a pocket of fluid is identified by ultrasound guidance after which a needle is advanced into this pocket. After insuring proper placement by withdrawing a small amount of fluid, the desired volume of fluid (Ringers lactate), defined by the number of weeks of gestational age times 10 millilitres, is infused manually. This procedure is repeated on a weekly basis if oligohydramnios re-occurs or persists.
If, after initial amnioinfusion, uterine contractions and signs of infection have been excluded, discharge is optional. Fluid retention will be assessed by measurement of SDP 48-72 hours after first amnioinfusion. Five to seven days after initial amnioinfusion, SDP is reassessed, as well as infection parameters (white cell count and CRP). Measurement of TC/AC, TC/FL, Doppler measurement, 3D lung volume measurement, will be performed by specialised personnel. If persisting or re-occurring oligohydramnios is diagnosed, amnioinfusion will be repeated. The same procedure will be repeated on a weekly basis until 28 weeks' gestation.
Patients randomised to expectant management will undergo the same clinical and ultrasound examination bi-weekly (once a week measurement of SDP, TC/AC, TC/FL, Doppler, 3D lung volume, infection parameters, and on the second weekly visit assessment of fetal well-being and measurement of SDP). These patients can, if signs of premature labour or infection have been excluded, at the discretion of the local physician, be discharged as well (Figure 8.1). All discharged patients will be instructed to take their temperature twice daily and contact the hospital in case of fever (temperature >37,8°C, rectally measured) or suspected infection. Patients with midtrimester PPROM are usually hospitalised after 24 weeks in a tertiary centre.

Use of co-intervention

Corticosteroids are given according to local protocol, usage will be recorded in the case report form. All patients will receive treatment with antibiotics (Erythromycin orally 250 mg 4 times per day for ten days)

Patients may stop participating in the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Study parameters / endpoints

We will compare two groups:
1) Amnioinfusion for midtrimester PPROM with oligohydramnios, and
2) Expectant management for midtrimester PPROM with oligohydramnios.

The primary outcome measure will be perinatal mortality, defined as intrauterine death, intrapartum death or neonatal death in the first 28 days of life.
Secondary outcomes are:

- Gestational age at delivery.
- Time from membrane rupture to delivery.
- Indication for delivery.
- Successful amnioinfusion (defined as retention of infused fluid as defined by a single deepest pocket of amniotic fluid of more than 2 cm for at least 48 hours).
- Placental abruption.
- Cord prolapse.
- Chorioamnionitis, (defined as fever before or during labour as a temperature greater than 37.5°C on two occasion more than one hour apart or a temperature > 38.0°C with either uterine tenderness (or contractions), leucocytosis, maternal or fetal tachycardia, or a foul-smelling vaginal discharge in absence of any other cause of hyperpyrexia).
- Fetal trauma due to puncture.
- Maternal length of stay in hospital

Occurrence of secondary outcomes placental abruption, cord prolapse, chorio-amnionitis and fetal trauma will be related to the number of amnioinfusions that have been performed.

Neonatal endpoints:

- Lethal pulmonary hypoplasia diagnosed according to radiological, clinical and pathological criteria. Pathological criteria are based on radial alveolar counts and lung/body weight ratios according to Askenazi and Perlman[9], when radial alveolar counts cannot be obtained, criteria by Wigglesworth et al will be used[10]. Clinical criteria used to diagnose lethal pulmonary hypoplasia are: immediate onset of severe respiratory insufficiency after birth, small lung capacity and requirement of high ventilatory pressures in the absence of obstruction or atelectasis. Radiological criteria according to Leonidas will be used[11].
- Non-lethal pulmonary hypoplasia diagnosed using same clinical and radiological criteria in surviving neonates.
- Survival till discharge from NICU.
- Neonatal mortality, defined as neonatal death in the first 28 days of life.
- Chronic lung disease (CLD), CLD defined as oxygen dependency at 28 days of life[12].
- Number of days on ventilatory support.
- Length of stay in hospital.
- Necrotising enterocolitis (NEC) more than stage I and defined according to the criteria of Bell et al.[13].

- Periventricular leukomalacia (PVL) more than grade I and defined according to the classification described by De Vries et al.[14].
- Severe intraventricular hemorrhage (IVH) more than grade II and defined according to the criteria of Papile et al [15].
- Proven neonatal sepsis defined as (1) Positive blood culture taken at birth or (2) within 72 hours two or more symptoms of infection (apnea, temperature instability, lethargy, feeding, intolerance, respiratory distress, hemodynamic instability) plus one of three items: (a) positive blood culture (culture proven sepsis); (b) CRP>20 (suspicion sepsis); (c) positive surface cultures of a known virulent pathogen (suspicion sepsis).

The neonatal endpoints will be defined by two neonatologists. The status of these endpoints will be evaluated at six months corrected age. Additional application for long-term follow-up of children (2 and 5 years) and mothers will be performed.

Safety reporting

This study has been approved by the ethics committee (METC) of the Academic Medical Centre Amsterdam and by the boards of management of all participating hospitals.
In accordance with the National Medical Research Act (WMO, Section 10, subsection 1), the investigator will inform the subjects and the reviewing accredited METC in case it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. All observed or volunteered adverse events, regardless of suspected causal relationship to the intervention, will be recorded.
An adverse event (AE) is defined as an event after which the intervention has to be stopped. Reasons for discontinuation are placental abruption, cord prolapse, chorioamnionitis, fetal loss, fetal trauma due to puncture, premature labour and delivery.
A serious adverse event (SAE) is defined as fetal or maternal death or illness necessitating IC or CCU treatment. All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC. In addition to the expedited reporting of SAE's, the principal investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC.
A Data Safety Monitoring Board (DSMB) will be established prior to start of the trial.

Sample size calculation

A sample size calculation was based on an expected rate of perinatal mortality of 70% with expectant management, to be reduced to 35% with amnioinfusion. Using a two-sided test, with a β-error of 0.20 and an α-error of 0.05 a sample size of 56 women (28 in each arm) is needed.

An interim analysis is planned after the follow up data of the first 28 women that have been included. The analysis will be performed using the O'Brien-Flemming alpha spending function meaning a nominal P value of less than 0.005 will be considered to indicate statistical significance[16]. If there is a significant difference in the primary outcome the trial will be stopped.

Statistical analysis

The analysis of the randomised clinical trial will be performed on an intention-to-treat principle. The differences between the amnioinfusion and expectant management will be assessed by calculating the ratio of the outcome rates in the two groups. Hence, the measure of association is a relative risk (RR) with a 95% confidence interval (CI), calculated using a log-binomial model. Time to delivery will be evaluated by Cox proportional hazard analysis, Kaplan-Meier estimates and tested with a log rank test.
In case of equivalence between outcomes, the analysis will be repeated on an "as-treated" basis. Subsequently, primary and secondary outcomes will be described in a subgroup of women with successful amnioinfusion (retention of infused fluid first 48 hours). All analyses will be adjusted for the fact that an interim analysis will be performed using the O'Brien-Flemming alpha spending function[16]. Consequently, a nominal P value of less than 0.049 will be considered to indicate statistical significance.

Discussion

There are signs that pregnancies complicated by oligohydramnios after midtrimester PPROM might benefit from amnioinfusion. However, currently there is insufficient evidence to recommend this procedure. The benefits might be increased neonatal survival and decreased pulmonary complications, especially pulmonary hypoplasia. Potential harms include placental abruption, premature labour and delivery, cord prolapse, chorioamnionitis, fetal loss, fetal trauma due to puncture. Of these, only the last mentioned is not a known potential complication of the underlying condition itself as well (midtrimester PPROM). Expectant management indeed carries these same risks. At present, there is no evidence on which a rational choice between expectant management or therapeutic amnioifusion can be based.

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Chapter 9

Concluding remarks and future perspectives

Concluding remarks and future perspectives

Midtrimester PPROM continues to be a challenging problem. High perinatal mortality and morbidity rates have been reported, and are mainly caused by prematurity, pulmonary hypoplasia and infection. Counseling parents is difficult since limited data are available. The data that are available are often from small retrospective studies, that are susceptible to selection bias and verification bias.
Counseling and clinical decision making is hindered by two unanswered questions. Firstly, it is not well known what the chance is of a short latency (and thus what are the chances of an extreme preterm birth), and secondly it is not known how longer latency affects outcome.
The mechanism that underlies the PPROM might give support in answering these questions, but is, at present usually unknown. It is proposed that there are four pathways causing preterm birth (see Figure 9.1, adapted from Lockwood), with or without PPROM. These are stress, inflammation, abruptio placentae, and pathologic uterine distension[1]. An intrinsic weakness of the membranes might also contribute to PPROM. Obviously there are mixed images.

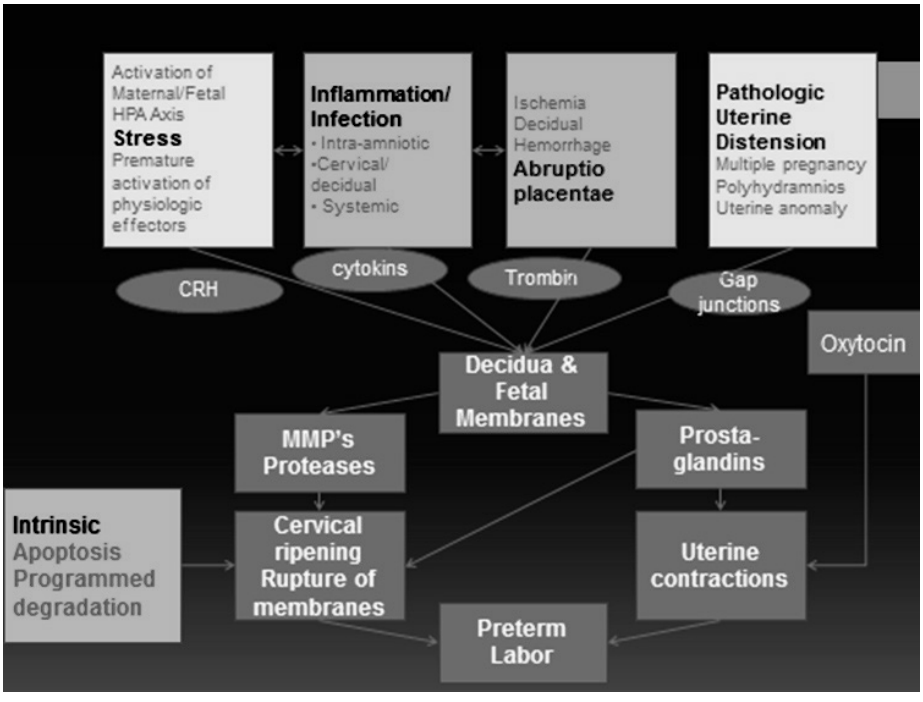

Figure 9.1 Pathways of preterm delivery adapted from Lockwood and Kuczynski[1].

Thus, for some pregnancies midtrimester PROM is a sign of antenatal exposure to intra-amniotic inflammation, whilst in other pregnancies inflammation seems to play a smaller role. It seems that inflammation in itself has an impact on outcome even without the existence of infection[2]. Infection might lead to inflammation and FIRS, with long-term neurological and respiratory damage for the newborn[3]. Furthermore a prolonged epsiode with oligohydramnios after midtrimester PPROM can lead to pulmonary hypoplasia. To investigate the impact of extended stay in utero, stratification of outcomes for gestational age at delivery can provide insight into the impact of latency on these outcomes.

With this intention, analysis of the Dutch perinatal registry (PRN) data in ***Chapter 2*** was done. This proved difficult as there is an important bias caused by the minimum gestational age at delivery of 22 weeks that is inherent to the PRN database. Yet there seems to be no obvious deterioration with longstanding PPROM if one compares groups with different gestational age at ROM who are born at the same gestational age. The data can be used when counseling women with PPROM who reach 22 weeks. Longer latency nor early gestational age should not be used as an argument to terminate the pregnancy. Before 22 weeks, expectant management is a reasonable course given the high percentage of morbidity free survival in the ones who do survive.

As illustrated in ***Chapter 3*** identification of patients with PPROM remains a sometimes difficult task. By using conventional methods the diagnosis is not clear in about 10% of cases. The review shows that the majority of studies carried out were not designed to answer the question that matters, namely, does equivocal fluid loss prove to be amniotic fluid or not. Furthermore it should be pointed out that it is not clear what the entity 'equivocal ruptured membranes' means in case of a true positive test. In the group of women with PPROM near term, it may have little relevance since expectant management seems preferable either way. However in the group with midtrimester PROM it is more likely that subclinical inflammation is involved. In this case an accurate diagnosis is likely to be more significant. New tests should be evaluated in this group (equivocal early PPROM), using a gold- or silver standard.

The PRN data in chapter 2, as well as unpublished data by van der Heyden, as well as extrapolated results of research by Manuck[4] provide indirect evidence that expectant management is generally associated with a better outcome for early cases of PROM. Considering the steep decrease in perinatal mortality after preterm birth between 24 and 28 weeks, this is not a surprise. If opting for expectant management, prediction of neonatal inflammation and infection and pulmonary hypoplasia is important.

In a retrospective cohort of patients with PPROM we assessed whether the C-reactive protein and Leucocytes were predictive of neonatal sepsis (***Chapter 4***). We found poor predictive capacity, and concluded that the decision to induce labour should not be based on these tests. This is in line with other reports. Indeed the role of monitoring CRP and leucocytes has not been established as useful in clinical practice[5,6]. Possibly there is a place for these tests in the context of a prediction model when multiple

variables are added as was done by van der Ham (van der Ham, van Kuijk, unpublished data).

The other clinically relevant question is whether lethal pulmonary hypoplasia is likely. In case of a positive test with a 100% positive predictive value, termination of pregnancy is justified. The metanalyses in ***Chapters 5 and 6*** in this paper show that there is only a very limited predictive value found from the available clinical data and currently used imaging techniques. As a single parameter, gestational age at rupture has the best predictive capacity at present, and scored better than the best ultrasound predictor. Therefore, as of yet, clinical practice and decision making should not be based on imaging parameters. A number of parameters combined offer possibilities as shown by Laudy and Tibboel et al.[7] and deserve further investigation. This will be examined in the ongoing PPROMEXIL - III trial. Should a combination of parameters have a sufficient predictive value, diagnosis should preferably be early in order to allow for a timely termination of pregnancy.

Considering the supposed pathophysiological mechanisms of disturbed pulmonary development through a decreased amount of amniotic fluid and risk of preterm labour, respiratory and neurological damage through presence of subclinical infection, it seems logical to infuse fluid in the amniotic cavity. Uncontrolled studies show a possible benefit, however, adequate proof through randomised controlled studies is currently absent as was reviewed for the Cochrane database (***Chapter 7***). Roberts et al. have started a trial in the UK, from which the results recently have been published. Their study compared weekly serial amnioinfusion with expectant management in women with oligohydramnios due to PPROM between 16 and 24 weeks gestation, with a minimum latency of 10 days. There was no difference in the primary outcome (perinatal mortality 19/28 vs. 19/28; RR 1.0; 95% CI0.70,1.43), maternal or neonatal morbidity. The observed difference in long term outcome (4/28 morbidity free survival at 2 years in the treatment group vs. 0/28) does not justify treatment, due to inadequate power, however it does justify further study[8]. In Italy there is a similar trial on-going[9]. In the Netherlands a randomised controlled trial – the PPROMEXIL-III study – was started. Meta-analysis of these trials will be done in the scheduled update of the Cochrane review.

The PPROMEXIL-III trial is conducted by the Dutch consortium, which provides an excellent infrastructure to answer clinical questions like this in a multicenter setting. After the upcoming reorganisation of the consortium hopefully such studies can continue to take place. The protocol of the PPROMEXIL-III study is outlined in ***Chapter 8***.

Recommendations for future research

Diagnosis of PPROM: new tests should preferably be evaluated in patients with equivocal early PPROM using a gold- or silver standard. In the same studies the prognosis of equivocal PPROM should be clarified and compared to overt PPROM.
There is a substantial percentage group of women with midtrimester PROM who are still pregnant after several weeks. At present it is not possible to identify fetuses who are at increased risk for extreme preterm birth, lethal pulmonary hypoplasia, or who are being damaged by on-going inflammation or infection during expectant management after PPROM.
A number of parameters (clinical as well as imaging) combined might identify patients at risk of lethal pulmonary hypoplasia. A combination of tests with 100% positive predictive value, early in pregnancy could allow for a timely termination of pregnancy.
Development of prediction models incorporating CRP and leucocytes as well as multiple other variables might identify fetuses at high risk of FIRS. In the future, biomarkers or new microbiological techniques which can predict this risk might become available. Proteomics can identify biomarkers of use, and might gain insight in the pathway that has led to the PPROM.
Distinct therapies, new, or already in use, might show benefit in smaller trials for these specific subgroups and subsequently may improve long term outcome after midtrimester PROM. Trials on serial amnioinfusion are being performed. (Individual Participant Data) Meta-analysis might answer the clinical question of their safety and efficacy. Obviously, non -traditional treatments have to be evaluated in a randomised controlled setting before being implemented.

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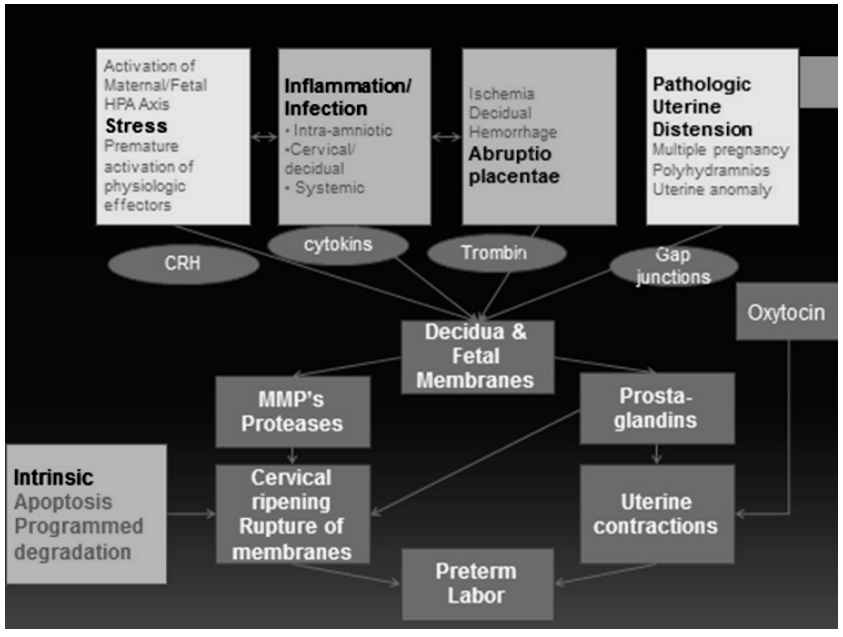
Conclusies en toekomstperspectieven

Conclusies en toekomstperspectieven

Midtrimester PPROM blijft een uitdagend probleem, gekenmerkt door hoge perinatale morbiditeit en mortaliteit. Deze worden vooral veroorzaakt door prematuriteit, longhypoplasie en infectie. Het counselen van ouders is moeilijk, omdat er onvoldoende gegevens beschikbaar zijn. De gegevens die beschikbaar zijn, komen vaak van kleine retrospectieve studies, die gevoelig zijn voor selectie- en verificatie bias.
Counseling en klinische besluitvorming wordt met name beperkt door twee onbeantwoorde vragen. Ten eerste is het niet bekend wat de kans is op een korte 'latency' – het interval tussen het breken van de vliezen en de partus - (en dus: wat zijn de kansen op een extreme vroeggeboorte), ten tweede is het niet bekend hoe een langere latency de uitkomst beïnvloedt.

Kennis van het mechanisme dat aan PPROM ten grondslag ligt zou kunnen helpen bij het beantwoorden van deze vragen, maar tot op heden is de oorzaak meestal onbekend. Verondersteld wordt dat er vier wegen zijn die leiden naar vroeggeboorte (zie afbeelding, gemodificeerd van Lockwood en Kuczynski), met of zonder PPROM. Deze zijn stress, inflammatie, abruptio placentae en uterine distensie[1]. Een intrinsieke zwakte van de vliezen kan ook bijdragen aan het ontstaan van PPROM. Uiteraard zijn er mengbeelden.



Pathways naar vroeggeboorte (gemodificeerd van Lockwood en Kuczynski[1])

Bij sommige zwangerschappen is midtrimester PROM dus een teken van prenatale blootstelling aan intra - amniotische inflammatie, terwijl in andere zwangerschappen inflammatie een kleinere rol lijkt te spelen. Het lijkt erop dat inflammatie op zich gevolgen heeft voor de uitkomst, zelfs zonder het bestaan van infectie[2].
Infectie kan leiden tot inflammatie en FIRS (fetal inflammatory respons syndrome) met ook op lange termijn neurologische schade en beschadiging van de luchtwegen[3]. Daarnaast kan een langdurige episode met oligohydramnios als gevolg van mid-trimester PPROM leiden tot *longhypoplasie*. Om de impact van een langdurig verblijf in de baarmoeder te onderzoeken, kan stratificatie van uitkomsten voor de factor 'zwangerschapsduur bij bevalling' inzicht geven in de impact van latency op deze uitkomsten.

Met dit voornemen, werden in hoofdstuk 2 gegevens van de Nederlandse perinatale registratie (PRN) geanalyseerd. Dit bleek moeilijk, aangezien de PRN database een zwangerschapsduur ten tijde van de geboorte van 22 weken als ondergrens kent. Dit levert een belangrijke bias op. Toch lijkt er geen duidelijke verslechtering met lang-durige PPROM te zijn als men groepen vergelijkt met verschillende zwangerschapsduur ten tijde van ROM, geboren met dezelfde zwangerschapsduur. De gegevens kunnen worden gebruikt bij het counselen van vrouwen met PPROM die 22 weken hebben bereikt. Langere latency noch vroege zwangerschapsduur ten tijde van ROM zouden geen argument moeten zijn om de zwangerschap af te breken. Vóór 22 weken is er uiteraard een aanzienlijke mortaliteit, echter een afwachtend beleid is toch een redelijke optie gezien het hoge percentage van morbiditeit-vrije overleving binnen de groep van overlevenden.

Hoofdstuk 3 illustreert het gegeven dat het stellen van de diagnose PPROM soms een moeilijke taak blijft. Door gebruik te maken van de conventionele methode blijft de diagnose onduidelijk in ongeveer 10% van de gevallen. Het review toont dat de meerderheid van de uitgevoerde studies niet werd ontworpen om de vraag te beantwoorden die er werkelijk toe doet, namelijk, is *twijfelachtig* vochtverlies vruchtwaterverlies of niet. Verder moet worden opgemerkt dat het niet duidelijk is wat de entiteit dubieus gebroken vliezen betekent in het geval van een juist positieve test. In de groep vrouwen met PPROM nabij de uitgerekende datum, zal het weinig relevantie hebben aangezien een afwachtend beleid hoe dan ook de voorkeur heeft. Maar in de groep met midtrimester PROM is het waarschijnlijker dat er een relatie met subklinische ontsteking is. In dit geval is een nauwkeurige diagnose mogelijk wel relevant. Nieuwe tests moeten worden geëvalueerd in deze groep (vroegtijdig dubieus gebroken vliezen), met een gouden of zilveren standaard.

De PRN gegevens in hoofdstuk 2, ongepubliceerde gegevens door van der Heyden, alsmede geëxtrapoleerde resultaten van onderzoek door Manuck et al.[4] leveren

indirect bewijs dat afwachtend beleid in het algemeen geassocieerd is met betere uitkomsten in geval van vroege PROM. Gezien de sterke daling van de perinatale mortaliteit na vroeggeboorte tussen 24 en 28 weken, is dit geen verrassing. Als de keuze voor een afwachtend beleid gemaakt is, wordt vervolgens de voorspelling van neonatale inflammatie en infectie en pulmonale hypoplasie belangrijk.
In een retrospectief cohort van patiënten met PPROM onderzochten we of het C-reactief proteïne (CRP) en leukocyten voorspellend waren voor neonatale sepsis (hoofdstuk 4). We vonden een zwak voorspellend vermogen, en concludeerden dat de beslissing om weeën op te wekken niet gebaseerd moet zijn op deze tests. Dit is in overeenkomst met reeds gepubliceerde bevindingen. De bruikbaarheid van CRP en leukocyten-controle is niet aangetoond in de klinische praktijk[5,6]. Mogelijk is er wel een plaats voor deze tests in het kader van een predictiemodel waarin meerdere variabele toegevoegd worden, zoals werd gedaan door van der Ham (Van der Ham, van Kuijk, ongepubliceerde data).
De andere klinisch relevante vraag is of er lethale longhypoplasie aanwezig is of gaat zijn. Bij een positieve test met een 100% positief voorspellende waarde is zwangerschapsafbreking gerechtvaardigd. Uit de metanalyses in de hoofdstukken 5 en 6 in dit document blijkt dat de beschikbare klinische gegevens en de momenteel gebruikte beeldvormende technieken slechts een zeer beperkte voorspellende waarde hebben. Op dit moment heeft de parameter ‘zwangerschap ten tijde van het breken van de vliezen’ de beste voorspellende waarde, deze scoorde beter dan de best voorspellende echo parameter. Daarom kunnen, op dit moment, klinische beslissingen niet genomen worden op basis van beeldvormende parameters. Een aantal parameters (klinische en beeldvormende) gecombineerd bieden wellicht mogelijkheden zoals werd beschreven door Laudy en Tibboel et al.[7] dit verdient nader onderzoek. Hier zal naar worden gekeken in de lopende PPROMEXIL - III trial. Indien een combinatie van parameters voldoende voorspellende waarde biedt, dient het diagnosticeren bij voorkeur vroeg in de zwangerschap plaats te vinden zodat een tijdige beëindiging van zwangerschap mogelijk is.

Gezien de veronderstelde pathofysiologische mechanismen van verstoorde pulmonale ontwikkeling als gevolg van een verminderde hoeveelheid vruchtwater en het risico van vroegtijdige partus, respiratoire en neurologische schade ten gevolge van de aanwezigheid van subklinische infectie, lijkt het logisch om vocht in de amnionholte te infunderen. Ongecontroleerde studies tonen een mogelijke voordeel, voldoende bewijs door gerandomiseerde gecontroleerde studies is momenteel echter afwezig. Dit werd beschreven in het Cochrane -review (hoofdstuk 7). Roberts et al. deden een trial in het Verenigd Koninkrijk, waarvan de resultaten onlangs zijn gepubliceerd. Hun studie vergeleek wekelijkse amnioinfusie met afwachtend beleid bij vrouwen met een oligohydramnion als gevolg van PPROM tussen de 16e en 24e week in de zwangerschap, met een minimale latency van 10 dagen. Er was geen verschil in de

primaire uitkomst (perinatale sterfte 19/28 versus 19/28 ; RR 1.0, 95 % CI0.70, 1.43), maternale of neonatale morbiditeit. Het waargenomen verschil in de lange termijn uitkomst (4/28 overleving zonder morbiditeit na 2 jaar in de behandelde groep versus 0/28) is vanwege onvoldoende power nog geen reden om amnioninfusie als behandeling in te voeren, maar het rechtvaardigt verder onderzoek[8]. In Italië is er een vergelijkbare trial aan de gang[9]. In Nederland werd een gerandomiseerde gecontroleerde trial - de PPROMEXIL - III studie - gestart. Meta - analyse van deze onderzoeken zal worden gedaan in de geplande update van het eerder genoemde Cochrane review.
De PPROMEXIL - III trial wordt uitgevoerd binnen het Nederlandse consortium, dat een uitstekende infrastructuur biedt om klinische vragen als deze te beantwoorden in een multicenter setting. Na de op handen zijnde reorganisatie van het consortium kunnen dergelijke studies hopelijk blijven plaatsvinden. Het protocol van de PPROMEXIL - III-studie wordt beschreven in hoofdstuk 8.

Aanbevelingen voor toekomstig onderzoek :
Diagnose van PPROM : nieuwe tests moeten bij voorkeur worden onderzocht bij patiënten met dubieus vroege PPROM, verificatie moet plaatsvinden met een gouden of zilveren standaard. In hetzelfde onderzoek moet de prognose van dubieus PPROM worden verduidelijkt en vergeleken worden met zekere PPROM.
Een aanzienlijke percentage van de vrouwen met midtrimester PROM is nog zwanger na enkele weken. Op dit moment is het niet mogelijk om foetussen te identificeren die een verhoogd risico lopen op extreme vroeggeboorte of lethale longhypoplasie, of die worden beschadigd door voortdurende ontsteking of infectie tijdens een afwachtend beleid na PPROM.
Een aantal parameters (zowel klinische als beeldvormende) gecombineerd zou patiënten met een risico op lethale longhypoplasie kunnen identificeren. Een combinatie van testen met een 100 % positief voorspellende waarde, vroeg in de zwangerschap zou een tijdige beëindiging van de zwangerschap mogelijk maken.
Ontwikkeling van predictiemodellen met CRP, leukocytengetal samen met andere variabelen zou foetussen kunnen identificeren met een hoog risico op FIRS. In de toekomst kunnen biomarkers of nieuwe microbiologische technieken die dit risico kan voorspellen beschikbaar. Technieken in de proteomica kunnen bruikbare biomarkers identificeren en wellicht inzicht bieden in de weg die heeft geleid tot PPROM.
Van specifieke therapieën, nieuwe, of reeds in gebruik zijnde, kan mogelijk voordeel worden aangetoond in kleinere studies voor deze specifieke subgroepen, en kunnen op lange termijn de uitkomst na midtrimester PROM verbeteren. Onderzoek naar seriële amnioinfusie wordt uitgevoerd. (Individual Patient Data-) Meta-analyse kan de klinische vraag met betrekking tot veiligheid en doeltreffendheid beantwoorden. Uiteraard moeten niet-traditionele behandelingen eerst worden geëvalueerd in een gerandomiseerd gecontroleerde setting alvorens zij kunnen worden toegepast.

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Dankwoord

Dankwoord

Velen ben ik dankbaar voor het tot stand komen van dit proefschrift. Hoewel de prospectieve data van de PPROMEXIL-III studie grotendeels nog moeten volgen is er een begin gemaakt en hoop ik met onderstaanden verder te mogen gaan in goede samenwerking.

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Curriculum vitae

Curriculum vitae

Stijn van Teeffelen werd op 5 april 1973 geboren in Utrecht. Hij behaalde zijn VWO diploma in 1991 op de Katholieke Scholengemeenschap de Breul te Zeist en startte de studie Geneeskunde aan de Universiteit van Utrecht. Het co-schap gynaecologie en obstetrie werd gevolgd in Bulawayo bij dr. D.A.A. Verkuyl, een onderzoeksstage bij de interne geneeskunde (dr. J.D. Banga), en een clerkship heelkunde in Stockholm. Na het behalen van het artsexamen startte hij, samen met Yvette van Horn, de opleiding tot tropenarts in 1999. In het kader hiervan werkte hij, als tropenarts in opleiding, als assistent gynaecologie en verloskunde in het st. Antoniusziekenhuis in Nieuwegein (opleider dr. J.H. Schagen van Leeuwen) en als assistent chirurgie in ziekenhuis Gooi Noord te Blaricum (opleider dr. H.P.N.W. Hoedemaker).
Na het behalen van het diploma in 2001 trouwde hij met Yvette van Horn en werd hij samen met haar door Voluntary Services Overseas (VSO) uitgezonden naar Ghana als tropenarts. Zij werkten daar in twee ziekenhuizen (St John of God ziekenhuis te Sefwi Asafo en St. Martins Hospital te Agroyesum). In 2003 keerden zij voor enkele maanden terug naar Groningen alwaar hun zoon Boris werd geboren.
In 2005 repatrieerden zij naar Utrecht, en kreeg hij een aanstelling als arts-assistent gynaecologie niet in opleiding in het Maxima Medisch Centrum te Veldhoven, Yvette kon beginnen aan de opleiding tot revalidatiearts. In 2006 werd hij aangenomen voor de opleiding Obstetrie en Gynaecologie in het cluster Maastricht (opleiders prof. G.G. Essed, prof. R.F. Kruitwagen). In dat zelfde jaar werd dochter Ella geboren. De eerste 4 jaar van de opleiding werd gevolgd in het Maxima (opleiders prof. S.G. Oei en dr. M.Y. Bongers), aldaar werd de basis voor dit proefschrift gelegd onder bezielende leiding van prof. B.W. Mol. In 2010 verhuisde het gezin naar Maastricht, voor de laatste 2 jaar van de opleiding. Na het afronden hiervan in 2012 kreeg hij een aanstelling als fellow perinatologie in Maastricht (opleider prof. J.G. Nijhuis), alwaar hij momenteel werkzaam is.

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